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<b>(54) Title:</b> SKIN LIGHTENING COMPOSITIONS  <b>(57) Abstract</b> <p>Topical compositions containing tocopherol sorbate which are useful for lightening skin are disclosed. Preferred compositions further contain an anti-inflammatory agent, an anti-oxidant/radical scavenger (preferably magnesium ascorbyl phosphate), and a retinoid. Preferred carriers include a long chain fatty alcohol and a polyethylene glycol ether thereof.</p>		

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## SKIN LIGHTENING COMPOSITIONS

### TECHNICAL FIELD

The subject invention relates to the field of skin lightening by application of compositions to the skin. The invention further relates to topical, skin lightening compositions containing tocopherol sorbate. The subject invention especially relates to methods of lightening hyperpigmented regions in skin by topical application of such compositions.

### BACKGROUND OF THE INVENTION

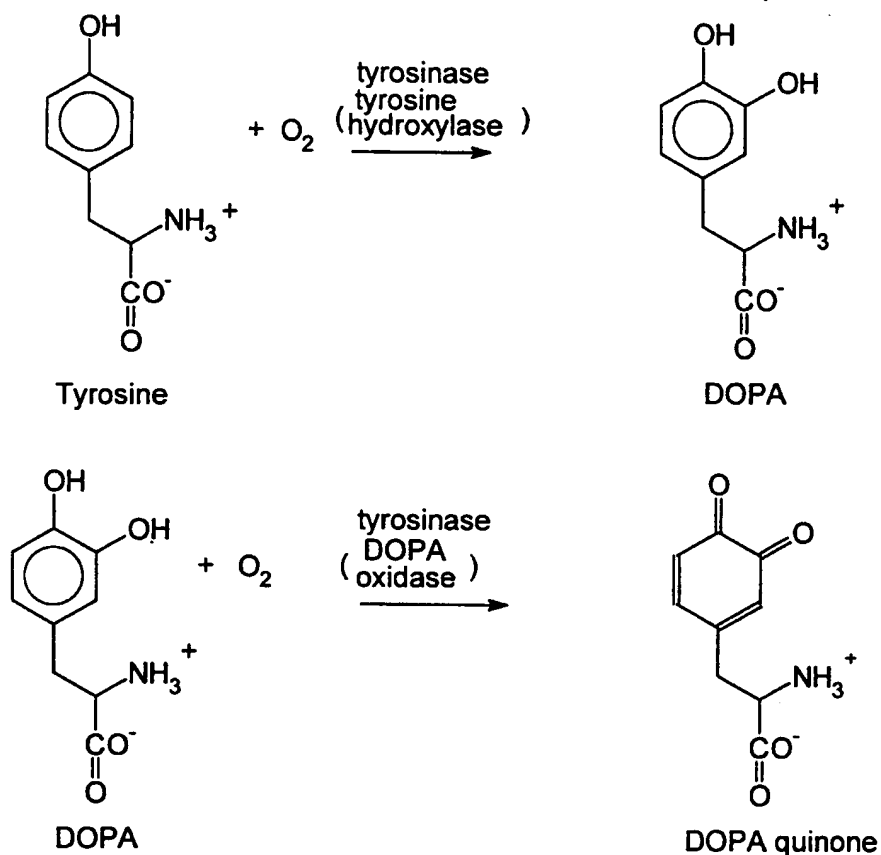
Many personal care products currently available to consumers are directed primarily to improving the health and/or physical appearance of the skin. Among these skin care products, many are directed to delaying, minimizing or even eliminating histological changes typically associated with the aging of skin or environmental damage to skin, e.g., skin wrinkling.

Skin is subject to insults by many extrinsic and intrinsic factors. Extrinsic factors include ultraviolet radiation (e.g., from sun exposure), heat, wind, low humidity, harsh surfactants, abrasives, and the like. Intrinsic factors include chronological aging and other biochemical changes from within the skin. Whether extrinsic or intrinsic, these factors result in visible and/or tactile signs of skin aging, such as wrinkling, sagging, inelasticity, sallowness, changes in skin pigmentation and other histological changes associated with skin aging. To many people, such changes are a reminder of the disappearance of youth. As a result, treatments directed to the amelioration of such signs have become a booming business in youth-conscious societies. Treatments range from cosmetic creams and moisturizers to various forms of cosmetic surgery.

These extrinsic or intrinsic factors, e.g., chronic exposure to UV light and chronological aging, may result in regions of hyperpigmentation in the skin. Certain forms of hyperpigmentation, e.g., freckles, age spots, liver spots, blotchiness, mottled pigmentation, and the like involving concentration of melanin in the skin, are believed to result from changes in the melanocytes and the keratinocytes present in the epidermis. Melanocytes, which are located at the base of the epidermis, lose their normal regulation process with aging and produce excess pigment. This excess production leads to the formation of dense perinuclear clumps of melanin in keratinocytes within the epidermis, resulting in areas of hyperpigmentation.

Traditional therapy for hyperpigmented skin includes the application of certain skin lightening agents, such as kojic acid, arbutin, hydroquinone or ascorbic acid, which inhibit melanin formation. A mechanism of action for these materials which has been proposed in the art is tyrosinase inhibition and/or inhibition of other steps in melanin synthesis. Tyrosinase is present within the melanosomes in epidermal melanocytes and catalyzes the committed step in the formation of melanin from tyrosine. See Goldsmith, L. A., Physiology, Biochemistry, and

Molecular Biology of the Skin, Oxford University Press, pp. 873-903 (N.Y. 1991). Tyrosinase catalyzes the hydroxylation of tyrosine and the oxidation of DOPA to DOPA quinone:



Binding of an inhibitor to the active site of tyrosinase results in decreased melanin formation. See generally Prota, G. Melanins and Melanogenesis, Academic Press, Inc., (San Diego 1992). The conversion of DOPA quinone to melanin occurs via non-enzymatic or spontaneous chemical reactions, some of which involve reactive oxygen or oxygen radicals.

Unfortunately, the efficacy of kojic acid and arbutin is marginal. Furthermore, hydroquinone has been associated with side effects due to cytotoxicity of the inhibitor's oxidized products. Ascorbic acid suffers from chemical stability problems and is therefore difficult to formulate into products having a shelf life needed for normal use.

Additionally, retinoic acid has been used to normalize the keratinocyte and melanocyte populations. Since melanocytes are under strong control of keratinocytes, normalized keratinocytes indirectly affect the pigment production by melanocytes. Retinoic acid also prevents pigment accumulation within the more rapidly dividing and migrating keratinocytes, and enhances the pigment-reducing ability of conventional skin lightening agents. However, the topical application of retinoic acid has been associated with skin irritation or retinoid dermatitis,

thus requiring careful control during use. Other retinoids have a lesser tendency for these disadvantages; unfortunately they tend to have less biological potency than retinoic acid.

WO95/34280, Greg. G. Hillebrand, published on December 21, 1995, describes the topical use of certain sulfhydryl compounds for lightening skin. The compositions can optionally contain an anti-oxidant/radical scavenger. Several compounds, including tocopherol sorbate, are listed as potential anti-oxidants/radical scavengers. The anti-oxidant/radical scavenger is disclosed to increase the skin lightening benefits of the composition.

Unfortunately, sulfhydryl compounds tend to suffer from the drawback of malodor, both in a formulation and once applied to the skin. Therefore, compositions containing sulfhydryl compounds generally must be formulated to minimize the occurrence or the user's detection of such odors. In addition, sulfhydryl compounds tend to be unstable in the presence of oxygen, thus requiring rigorous removal of oxygen during the formulation process.

There is therefore a need for the development of skin lightening agents that are more efficacious, safer, and more easily formulated than available agents.

It has now been found that topical compositions containing tocopherol sorbate and which do not contain a sulfhydryl compound are useful for lightening skin, especially hyperpigmented regions of skin. It has further been found that topical compositions containing tocopherol sorbate, an anti-inflammatory agent, an anti-oxidant (especially an ascorbic acid derivative) and a retinoid are particularly effective for lightening skin.

It is therefore an object of the present invention to provide topical compositions containing tocopherol sorbate for lightening mammalian skin (especially human skin, more especially human facial and hand skin).

It is another object of the present invention to provide topical compositions for lightening mammalian skin (especially human skin, more especially human facial and hand skin), containing tocopherol sorbate, an anti-inflammatory agent, an anti-oxidant and a retinoid.

It is another object of the present invention to provide such compositions wherein the composition contains a physically stable, oil-in-water emulsion, especially an emulsion containing a nonionic polyethylene glycol ether of the formula  $\text{CH}_3(\text{CH}_2)_m\text{CH}_2(\text{OCH}_2\text{CH}_2)_n(\text{OH})$ , wherein "m" is an integer greater than about 10 and "n" is on average an integer greater than about 10; and a fatty alcohol of the formula  $\text{CH}_3(\text{CH}_2)_p\text{CH}_2\text{OH}$ , wherein "p" is an integer greater than about 10.

These and other objects of this invention will become apparent in light of the following disclosure.

#### SUMMARY OF THE INVENTION

The present invention relates to topical compositions containing tocopherol sorbate, which are useful for lightening skin. Preferred compositions contain tocopherol sorbate, an anti-

inflammatory agent, an anti-oxidant/radical scavenger, a retinoid and a topical carrier. In a particularly preferred embodiment, the anti-oxidant/radical scavenger is magnesium ascorbyl phosphate. The topical carrier is preferably in the form of an oil-in-water emulsion, more preferably comprising (a) a saturated fatty alcohol of the formula  $\text{CH}_3(\text{CH}_2)_p\text{CH}_2\text{OH}$ , wherein  $p$  is an integer greater than about 10, and (b) an ethoxylated ether of a saturated fatty alcohol having the formula  $\text{CH}_3(\text{CH}_2)_m\text{CH}_2(\text{OCH}_2\text{CH}_2)_n\text{OH}$ , wherein " $m$ " is an integer greater than about 10 and " $n$ " (the average number of moles ethylene oxide) is on average an integer greater than about 10. Especially preferred fatty alcohols are selected from stearyl alcohol, cetyl alcohol and cetearyl alcohol; especially preferred ethers are selected from Cetareth- $n$ , Steareth- $n$ , and Ceteth- $n$ .

The invention further relates to methods of lightening skin, e.g., lightening hyperpigmented regions of skin, and of lightening skin by regulating melanin in skin.

#### DETAILED DESCRIPTION OF THE INVENTION

It has been unexpectedly found that tocopherol sorbate achieves skin lightening, including lightening of hyperpigmented regions in mammalian skin, when applied topically to the skin in the absence of a sulfhydryl compound. The subject invention is not limited to any particular mechanism of action, but is believed to operate by the inhibition of oxidative processes involved in the non-enzymatic steps in melanin production and/or by preventing reactive oxygen/oxygen radical stimulation (oxidative stress) of melanocytes which results in initiation of the melanin production pathway within the melanocytes, e.g., which can occur with UV or sunlight exposure. Compositions of this invention preferably contain from or about 0.01% to or about 10%, of tocopherol sorbate, more preferably from or about 0.05% to or about 5%, most preferably from or about 0.1% to or about 5%, e.g., 2%, tocopherol sorbate.

All percentages and ratios used herein are by weight of the total composition and all measurements made are at 25°C, unless otherwise specified.

The compositions of the present invention can comprise, consist essentially of, or consist of, the essential as well as optional ingredients and components described herein. As used herein, "consisting essentially of" means that the composition or component may include additional ingredients, but only if the additional ingredients do not materially alter the basic and novel characteristics of the claimed compositions or methods. As used herein, "consisting essentially of" means that the component or composition described by that phrase does not contain a sulfhydryl compound.

All publications cited herein are hereby incorporated by reference in their entirety.

The term "topical application", as used herein, means to apply or spread the compositions of the present invention onto the surface of the skin. Preferred compositions of the present invention are those in a form intended to be left in contact with the skin for an extended

period (e.g., for several hours) after topical application, e.g., typical usage of a cream, lotion, moisturizer or the like.

The term "dermatologically-acceptable," as used herein, means that the compositions or components thereof so described are suitable for use in contact with human skin without undue toxicity, incompatibility, instability, allergic response, and the like.

The term "safe and effective amount" as used herein means an amount of a compound or composition sufficient to significantly induce the intended benefit, but low enough to avoid serious side effects, i.e., to provide a reasonable benefit to risk ratio, within the scope of sound judgment of the skilled artisan.

The compositions of the present invention are useful for regulating signs of skin aging, especially visible and/or tactile discontinuities in skin appearance or texture associated with aging. "Regulating the signs of skin aging" includes prophylactically regulating and/or therapeutically regulating one or more of such signs. As used herein, prophylactically regulating such signs includes delaying, minimizing and/or preventing the occurrence of undesired signs of skin aging. As used herein, therapeutically regulating such signs includes diminishing, minimizing and/or effacing existing, undesired signs of skin aging.

"Signs of skin aging" include, but are not limited to, all outward visibly and tactilely perceptible manifestations as well as any other macro or micro effects due to skin aging. Such signs may be induced or caused by intrinsic factors or extrinsic factors, e.g., chronological aging and/or environmental damage. These signs may result from processes which include, but are not limited to, the development of hyperpigmented regions, discoloration (including undereye circles), sallowness, textural discontinuities such as wrinkles, including both fine superficial wrinkles and coarse deep wrinkles, skin lines, crevices, bumps, large pores, altered texture, and/or other forms of skin unevenness or roughness, loss of skin elasticity (loss and/or inactivation of functional skin elastin), sagging (including puffiness in the eye area, and jowls), loss of skin firmness, loss of skin tightness, loss of skin recoil from deformation, keratoses, hyperkeratinization, altered exfoliation or desquamation, elastosis, collagen breakdown, and other histological changes in the stratum corneum, dermis, epidermis, the skin vascular system (e.g., telangiectasia or spider vessels), and underlying tissues (e.g., loss of subcutaneous fat or development of cellulite), especially those proximate to the skin.

The compositions of the present invention are especially useful for regulating skin pigmentation associated with melanin. As used herein, regulating skin pigmentation includes skin lightening. Skin lightening involves diminishing, minimizing and/or effacing existing melanin in skin (therapeutic), and/or delaying, minimizing and/or preventing the formation of melanin in skin (prophylactic), including hyperpigmented regions of skin. As used herein "hyperpigmented region" means a localized region of high melanin content including age spots.

liver spots, blotchiness, mottling, melasma, chloasma, freckles, post inflammatory hyperpigmentation or sun-induced pigmented blemishes.

#### Carrier

The compositions of the present invention preferably contain a dermatologically acceptable carrier within which the tocopherol sorbate and optional other actives are incorporated to enable the actives to be delivered to the skin at an appropriate concentration. The carrier can thus act as a diluent, dispersant, solvent, or the like for the actives which ensures that it can be applied to and distributed evenly over the selected target at an appropriate concentration.

The carrier may contain one or more dermatologically acceptable solid, semi-solid or liquid fillers, diluents, solvents, extenders and the like. The carrier may be solid, semi-solid or liquid. The carrier can itself be inert or it can possess dermatological benefits of its own. Concentrations of the carrier can vary with the carrier selected and the intended concentrations of the essential and optional components.

Suitable carriers for use in the compositions include conventional or otherwise known carriers that are dermatologically acceptable. The carrier should also be physically and chemically compatible with the essential components described herein, and should not unduly impair stability, efficacy or other use benefits associated with the compositions of the present invention. Preferred components of the compositions of this invention should be capable of being comingled in a manner such that there is no interaction which would substantially reduce the efficacy of the composition under ordinary use situations.

The type of carrier utilized in the present invention depends on the type of product form desired for the composition. The topical compositions useful in the subject invention may be made into a wide variety of product forms such as are known in the art. These include, but are not limited to, lotions, creams, gels, sticks, sprays, ointments, pastes, mousses, cleansers, and cosmetics (e.g., solid, semi-solid, or liquid make-up, including foundations, eye-makeup, lipsticks and the like). These product forms may comprise several types of carriers including, but not limited to, solutions, aerosols, emulsions, gels, solids, and liposomes.

Preferred carriers contain a dermatologically acceptable, hydrophilic diluent. As used herein, "diluent" includes materials in which the actives can be dispersed, dissolved, or otherwise incorporated. Hydrophilic diluents include water, organic hydrophilic diluents such as lower monovalent alcohols (e.g., C<sub>1</sub> - C<sub>4</sub>) and low molecular weight glycols and polyols, including propylene glycol, polyethylene glycol (e.g., Molecular Weight 200-600 g/mole), polypropylene glycol (e.g., Molecular Weight 425-2025 g/mole), glycerol, butylene glycol, 1,2,4-butanetriol, sorbitol esters, 1,2,6-hexanetriol, ethanol, isopropanol, sorbitol esters, butanediol, ether propanol, ethoxylated ethers, propoxylated ethers and combinations thereof.



Water is a preferred diluent. The composition preferably comprises from about 70% to about 99.99% of the hydrophilic diluent. The compositions may additionally or alternatively include a hydrophobic diluent.

Solutions according to the subject invention typically include a dermatologically acceptable hydrophilic diluent. Solutions useful in the subject invention preferably contain from about 70% to about 99.99% of the hydrophilic diluent.

Aerosols according to the subject invention can be formed by adding a propellant to a solution such as described above. Exemplary propellants include chloro-fluorinated lower molecular weight hydrocarbons. Additional propellants that are useful herein are described in Sagarin, Cosmetics Science and Technology, 2nd Edition, Vol. 2, pp. 443-465 (1972), incorporated herein by reference. Aerosols are typically applied to the skin as a spray-on product.

Preferred carriers comprise an emulsion such as oil-in-water emulsions, water-in-oil emulsions, and water-in-silicone emulsions, with oil-in-water emulsions and water-in-silicone emulsions being more preferred. As will be understood by the skilled artisan, a given component will distribute into either the water or oil/silicone phase depending on the water solubility/dispersibility of the component in the composition.

Emulsions according to the present invention generally contain a solution as described above and a lipid or oil. Lipids and oils may be derived from animals, plants, or petroleum and may be natural or synthetic. Preferred emulsions also contain a humectant, such as glycerol. Emulsions will preferably further contain from about 1% to about 10%, more preferably from about 2% to about 5%, of an emulsifier or surfactant, based on the weight of the carrier. Emulsifiers/surfactants may be nonionic, anionic, cationic, zwitterionic or amphoteric. Suitable emulsifiers and surfactants are disclosed in, for example, U.S. Patent 3,755,560, issued August 28, 1973, Dickert et al.; U.S. Patent 4,421,769, issued December 20, 1983, Dixon et al.; and McCutcheon's Detergents and Emulsifiers, North American Edition, pages 317-324 (1986), each incorporated herein by reference.

The emulsion may also contain an anti-foaming agent to minimize foaming upon application to the skin. Anti-foaming agents include high molecular weight silicones and other materials well known in the art for such use.

Suitable emulsions may have a wide range of viscosities, depending on the desired product form. Exemplary low viscosity emulsions have a viscosity of about 50 centistokes or less, more preferably about 10 centistokes or less, most preferably about 5 centistokes or less.

Preferred oil-in-water emulsions and water-in-silicone emulsions are described in greater detail below.

**a) Oil-in-Water Emulsions**

Oil-in-water emulsions have a continuous aqueous phase and a hydrophobic, water-insoluble phase dispersed therein ("oil phase", which is the "dispersed phase") (In emulsion technology, the term "dispersed phase" is a term well-known to one skilled in the art which means that the phase exists as small particles or droplets that are suspended in and surrounded by a continuous phase. The dispersed phase is also known as the internal or discontinuous phase.) As will be understood by those skilled in the art, the tocopherol sorbate distributes primarily into the oil phase. Other materials such as described herein may also be incorporated into one or both of these phases and distribute primarily in a given phase depending on their solubility or dispersibility in that phase. An especially preferred oil-in-water emulsion, containing a structuring agent, a surfactant and water, is described in detail hereinafter.

(i) Structuring Agent

A preferred oil-in-water emulsion comprises a structuring agent to assist, e.g., in building viscosity or in the formation of a liquid crystalline gel network structure. The structuring agent may also act as an emulsifier or surfactant. Concentrations of such structuring agents are from or about 1% to or about 20%, preferably from or about 1% to or about 10%, more preferably from or about 3% to or about 9% by weight of the carrier.

Suitable structuring agents include saturated fatty alcohols of the formula  $\text{CH}_3(\text{CH}_2)_p\text{CH}_2\text{OH}$ , wherein "p" is a positive integer, preferably an integer greater than about 10, more preferably at least about 12, most preferably from about 14 to about 28, e.g., from 14 to 16. Also useful are ethoxylated ethers of saturated fatty alcohols having the formula  $\text{CH}_3(\text{CH}_2)_m\text{CH}_2(\text{OCH}_2\text{CH}_2)_n\text{OH}$ , wherein "m" is a positive integer, preferably an integer greater than about 10, more preferably at least about 12, most preferably from about 14 to about 28, e.g., from 14 to 16; and "n" (the average number of moles ethylene oxide) is from about 1 to about 5. Saturated  $\text{C}_{16}$  to  $\text{C}_{30}$  diols, saturated  $\text{C}_{16}$  to  $\text{C}_{30}$  monoglycerol ethers, and saturated  $\text{C}_{16}$  to  $\text{C}_{30}$  hydroxy fatty acids are also useful. Suitable structuring agents have a melting point of at least about  $45^\circ\text{C}$ . Mixtures of the foregoing can be used.

Preferred structuring agents include stearyl alcohol, cetyl alcohol, cetearyl alcohol, myristyl alcohol, behenyl alcohol, stearic acid, palmitic acid, the polyethylene glycol ether of stearyl alcohol having an average of from about 1 to about 5 ethylene oxide units (e.g., Steareth-2, available under the tradename of Brij® 72 from ICI Americas, having an average of about 2 ethylene oxide units), the polyethylene glycol ether of cetyl alcohol having an average of from about 1 to about 5 ethylene oxide units, and mixtures thereof. More preferred structuring agents of the present invention are selected from the group consisting of stearyl alcohol, cetyl alcohol, cetearyl alcohol, myristyl alcohol, behenyl alcohol, and mixtures thereof. Most preferred are stearyl alcohol, cetyl alcohol and cetearyl alcohol.

(ii) Surfactant

Preferred oil-in-water emulsions contain a surfactant. Concentrations of the surfactant are generally from or about 0.05% to or about 10%, preferably from or about 1% to or about 6%, more preferably from or about 1% to or about 3% by weight of the carrier.

Among the surfactants useful herein are various non-ionic and anionic surfactants such as alkoxyated ethers of C1-C30 fatty alcohols (preferably ethoxylated ethers of saturated fatty alcohols having the formula  $\text{CH}_3(\text{CH}_2)_m\text{CH}_2(\text{OCH}_2\text{CH}_2)_n\text{OH}$ , wherein "m" is a positive integer, preferably an integer greater than about 10, more preferably at least about 12, even more preferably from about 14 to about 28, most preferably 14-16; and "n" (the average number of moles ethylene oxide) is a positive integer, preferably at least about about 5, more preferably at least about 10, even more preferably at least about 12, most preferably from about 16 to about 55, sugar esters and polyesters, alkoxyated sugar esters and polyesters, C1-C30 fatty acid esters of C1-C30 fatty alcohols, alkoxyated derivatives of C1-C30 fatty acid esters of C1-C30 fatty alcohols, polyglyceryl esters of C1-C30 fatty acids, C1-C30 esters of polyols, C1-C30 ethers of polyols, alkyl phosphates, polyoxyalkylene fatty ether phosphates, fatty acid amides, acyl lactylates, soaps, and mixtures thereof. Other suitable surfactants are described, for example, in McCutcheon's, Detergents and Emulsifiers, North American Edition (1986), published by Allured Publishing Corporation; U.S. Patent No. 5,011,681 to Ciotti et al., issued April 30, 1991; U.S. Patent No. 4,421,769 to Dixon et al., issued December 20, 1983; and U.S. Patent No. 3,755,560 to Dickert et al., issued August 28, 1973; these references are incorporated herein by reference in their entirety.

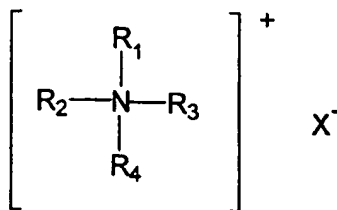
Nonlimiting examples of these surfactants include: Cetareth-n (wherein "n" has the values stated above, commercially available, e.g., from ICI Surfactants (Wilmington, Delaware), under the tradename Brij; e.g., Cetareth-20 (Brij 68), ethoxylated ether of cetearyl alcohol, having an average of 20 moles ethylene oxide); Steareth-n (wherein "n" has the values stated above, commercially available, e.g., from ICI Surfactants under the tradename Brij; e.g., Steareth-20, ethoxylated ether of stearyl alcohol, having an average of 20 moles ethylene oxide); Ceteth-n (wherein "n" has the values stated above, commercially available, e.g., from ICI Surfactants under the tradename Brij; e.g., Ceteth-20, ethoxylated ether of cetyl alcohol, having an average of 20 moles ethylene oxide); polyethylene glycol 20 sorbitan monolaurate (Polysorbate 20), polyethylene glycol 5 soya sterol, PPG-2 methyl glucose ether distearate, Polysorbate 80, cetyl phosphate, potassium cetyl phosphate, diethanolamine cetyl phosphate, Polysorbate 60, glyceryl stearate, PEG-100 stearate, polyoxyethylene 20 sorbitan trioleate (Polysorbate 85), sorbitan monolaurate, polyoxyethylene 4 lauryl ether sodium stearate, polyglyceryl-4 isostearate, hexyl laurate, and mixtures thereof.

A particularly preferred composition of the present invention contains a structuring agent selected from saturated fatty alcohols (preferably of the formula  $\text{CH}_3(\text{CH}_2)_p\text{CH}_2\text{OH}$ , wherein "p" is an integer greater than about 10, preferably at least about 12, more preferably from about 14 to about 28, e.g., from 14 to 16); and a surfactant selected from ethoxylated ethers of saturated fatty alcohols (preferably having the formula  $\text{CH}_3(\text{CH}_2)_m\text{CH}_2(\text{OCH}_2\text{CH}_2)_n\text{OH}$ , wherein "m" is an integer greater than about 10, preferably at least about 12, more preferably from about 14 to about 28, even more preferably 14-16; and "n" is on average an integer greater than about 10, preferably at least about 12, more preferably from about 16 to about 55). Such a combination is particularly effective in physically stabilizing a preferred composition of the invention containing an electrolyte, e.g., metal salts (e.g., Ca, Mn, Mg, Na, K, Al, Zn salts), e.g., such salts of ascorbyl phosphates, sulfates and carbonates, (e.g., magnesium ascorbyl phosphate). Even more preferred are compositions containing a structuring agent selected from stearyl alcohol, cetyl alcohol, cetearyl alcohol, myristyl alcohol, and mixtures thereof, and the surfactant Cetareth-n ( $n > \text{about } 10$ ), Steareth-n ( $n > \text{about } 10$ ), and Ceteth-n ( $n > \text{about } 10$ ). Oil-in-water emulsions containing the foregoing combinations of structuring agent and surfactant preferably comprise at least about 1% of the surfactant and at least about 3% of the structuring agent.

Other suitable surfactants include any of a wide variety of known cationic, anionic, zwitterionic, and amphoteric surfactants. See McCutcheon's, Detergents and Emulsifiers, North American Edition (1986), published by Allured Publishing Corporation; U.S. Patent 5,011,681; U.S. Patent 4,421,769; and U.S. Patent 3,755,560; these references are incorporated herein by reference in their entirety.

The exact surfactant chosen will depend upon the pH of the composition and the other components present.

Preferred are cationic surfactants, especially dialkyl quaternary ammonium compounds, examples of which are described in U.S. Patent 5,151,209; U.S. Patent 5,151,210; U.S. Patent 5,120,532; U.S. Patent 4,387,090; U.S. Patent 3,155,591; U.S. Patent 3,929,678; U.S. Patent 3,959,461; McCutcheon's, Detergents & Emulsifiers, (North American edition 1979) M.C. Publishing Co.; and Schwartz, et al., Surface Active Agents, Their Chemistry and Technology, New York: Interscience Publishers, 1949; which descriptions are incorporated herein by reference. The cationic surfactants useful herein include cationic ammonium salts such as those having the formula:



wherein  $R_1$ , is an alkyl group having from about 12 to about 30 carbon atoms, or an aromatic, aryl or alkaryl group having from about 12 to about 30 carbon atoms;  $R_2$ ,  $R_3$ , and  $R_4$  are independently selected from hydrogen, an alkyl group having from about 1 to about 22 carbon atoms, or aromatic, aryl or alkaryl groups having from about 12 to about 22 carbon atoms; and  $X$  is any compatible anion, preferably selected from the group consisting of chloride, bromide, iodide, acetate, phosphate, nitrate, sulfate, methyl sulfate, ethyl sulfate, tosylate, lactate, citrate, glycolate, and mixtures thereof. Additionally, the alkyl groups of  $R_1$ ,  $R_2$ ,  $R_3$ , and  $R_4$  can also contain ester and/or ether linkages, or hydroxy or amino group substituents (e.g., the alkyl groups can contain polyethylene glycol and polypropylene glycol moieties).

More preferably,  $R_1$  is an alkyl group having from about 12 to about 22 carbon atoms;  $R_2$  is selected from H or an alkyl group having from about 1 to about 22 carbon atoms;  $R_3$  and  $R_4$  are independently selected from H or an alkyl group having from about 1 to about 3 carbon atoms; and  $X$  is as described previously.

Most preferably,  $R_1$  is an alkyl group having from about 12 to about 22 carbon atoms;  $R_2$ ,  $R_3$ , and  $R_4$  are selected from H or an alkyl group having from about 1 to about 3 carbon atoms; and  $X$  is as described previously.

Alternatively, other useful cationic emulsifiers include amino-amides, wherein in the above structure  $R_1$  is alternatively  $R_5\text{CONH}-(\text{CH}_2)_n$ , wherein  $R_5$  is an alkyl group having from about 12 to about 22 carbon atoms, and  $n$  is an integer from about 2 to about 6, more preferably from about 2 to about 4, and most preferably from about 2 to about 3. Nonlimiting examples of these cationic emulsifiers include stearamidopropyl PG-dimonium chloride phosphate, behenamidopropyl PG dimonium chloride, stearamidopropyl ethyldimonium ethosulfate, stearamidopropyl dimethyl (myristyl acetate) ammonium chloride, stearamidopropyl dimethyl cetearyl ammonium tosylate, stearamidopropyl dimethyl ammonium chloride, stearamidopropyl dimethyl ammonium lactate, and mixtures thereof. Especially preferred is behenamidopropyl PG dimonium chloride.

Nonlimiting examples of quaternary ammonium salt cationic surfactants include those selected from the group consisting of cetyl ammonium chloride, cetyl ammonium bromide, lauryl ammonium chloride, lauryl ammonium bromide, stearyl ammonium chloride, stearyl ammonium bromide, cetyl dimethyl ammonium chloride, cetyl dimethyl ammonium bromide, lauryl dimethyl ammonium chloride, lauryl dimethyl ammonium bromide, stearyl dimethyl

ammonium chloride, stearyl dimethyl ammonium bromide, cetyl trimethyl ammonium chloride, cetyl trimethyl ammonium bromide, lauryl trimethyl ammonium chloride, lauryl trimethyl ammonium bromide, stearyl trimethyl ammonium chloride, stearyl trimethyl ammonium bromide, lauryl dimethyl ammonium chloride, stearyl dimethyl cetyl ditallow dimethyl ammonium chloride, dicetyl ammonium chloride, dicetyl ammonium bromide, dilauryl ammonium chloride, dilauryl ammonium bromide, distearyl ammonium chloride, distearyl ammonium bromide, dicetyl methyl ammonium chloride, dicetyl methyl ammonium bromide, dilauryl methyl ammonium chloride, dilauryl methyl ammonium bromide, distearyl methyl ammonium chloride, distearyl methyl ammonium bromide, and mixtures thereof. Additional quaternary ammonium salts include those wherein the C<sub>12</sub> to C<sub>30</sub> alkyl carbon chain is derived from a tallow fatty acid or from a coconut fatty acid. The term "tallow" refers to an alkyl group derived from tallow fatty acids (usually hydrogenated tallow fatty acids), which generally have mixtures of alkyl chains in the C<sub>16</sub> to C<sub>18</sub> range. The term "coconut" refers to an alkyl group derived from a coconut fatty acid, which generally have mixtures of alkyl chains in the C<sub>12</sub> to C<sub>14</sub> range. Examples of quaternary ammonium salts derived from these tallow and coconut sources include ditallow dimethyl ammonium chloride, ditallow dimethyl ammonium methyl sulfate, di(hydrogenated tallow) dimethyl ammonium chloride, di(hydrogenated tallow) dimethyl ammonium acetate, ditallow dipropyl ammonium phosphate, ditallow dimethyl ammonium nitrate, di(coconutalkyl)dimethyl ammonium chloride, di(coconutalkyl)dimethyl ammonium bromide, tallow ammonium chloride, coconut ammonium chloride, stearamidopropyl PG-dimonium chloride phosphate, stearamidopropyl ethyldimonium ethosulfate, stearamidopropyl dimethyl (myristyl acetate) ammonium chloride, stearamidopropyl dimethyl cetearyl ammonium tosylate, stearamidopropyl dimethyl ammonium chloride, stearamidopropyl dimethyl ammonium lactate, and mixtures thereof. An example of a quaternary ammonium compound having an alkyl group with an ester linkage is ditallowyl oxyethyl dimethyl ammonium chloride.

More preferred cationic surfactants are those selected from the group consisting of behenamidopropyl PG dimonium chloride, dilauryl dimethyl ammonium chloride, distearyl dimethyl ammonium chloride, dimyristyl dimethyl ammonium chloride, dipalmityl dimethyl ammonium chloride, distearyl dimethyl ammonium chloride, stearamidopropyl PG-dimonium chloride phosphate, stearamidopropyl ethyldiammonium ethosulfate, stearamidopropyl dimethyl (myristyl acetate) ammonium chloride, stearamidopropyl dimethyl cetearyl ammonium tosylate, stearamidopropyl dimethyl ammonium chloride, stearamidopropyl dimethyl ammonium lactate, and mixtures thereof.

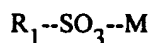
Most preferred cationic surfactants are those selected from the group consisting of behenamidopropyl PG dimonium chloride, dilauryl dimethyl ammonium chloride, distearyl

dimethyl ammonium chloride, dimyristyl dimethyl ammonium chloride, dipalmityl dimethyl ammonium chloride, and mixtures thereof.

A preferred combination of cationic surfactant and structuring agent is behenamidopropyl PG dimonium chloride and/or behenyl alcohol, wherein the ratio is preferably optimized to maintained to enhance physical and chemical stability, especially when such a combination contains ionic and/or highly polar solvents. This combination is especially useful for delivery of sunscreens agents such as zinc oxide and octyl methoxycinnamate.

A wide variety of anionic surfactants are also useful herein. See, e.g., U.S. Patent No. 3,929,678, to Laughlin et al., issued December 30, 1975, which is incorporated herein by reference in its entirety. Nonlimiting examples of anionic surfactants include the alkoyl isethionates, and the alkyl and alkyl ether sulfates. The alkoyl isethionates typically have the formula  $\text{RCO-OCH}_2\text{CH}_2\text{SO}_3\text{M}$  wherein R is alkyl or alkenyl of from about 10 to about 30 carbon atoms, and M is a water-soluble cation such as ammonium, sodium, potassium and triethanolamine. Nonlimiting examples of these isethionates include those alkoyl isethionates selected from the group consisting of ammonium cocoyl isethionate, sodium cocoyl isethionate, sodium lauroyl isethionate, sodium stearyl isethionate, and mixtures thereof.

The alkyl and alkyl ether sulfates typically have the respective formulae  $\text{ROSO}_3\text{M}$  and  $\text{RO}(\text{C}_2\text{H}_4\text{O})_x\text{SO}_3\text{M}$ , wherein R is alkyl or alkenyl of from about 10 to about 30 carbon atoms, x is from about 1 to about 10, and M is a water-soluble cation such as ammonium, sodium, potassium and triethanolamine. Another suitable class of anionic surfactants are the water-soluble salts of the organic, sulfuric acid reaction products of the general formula:



wherein  $\text{R}_1$  is chosen from the group consisting of a straight or branched chain, saturated aliphatic hydrocarbon radical having from about 8 to about 24, preferably about 10 to about 16, carbon atoms; and M is a cation. Still other anionic synthetic surfactants include the class designated as succinamates, olefin sulfonates having about 12 to about 24 carbon atoms, and  $\beta$ -alkyloxy alkane sulfonates. Examples of these materials are sodium lauryl sulfate and ammonium lauryl sulfate.

Other anionic materials useful herein are soaps (i.e. alkali metal salts, e.g., sodium or potassium salts) of fatty acids, typically having from about 8 to about 24 carbon atoms, preferably from about 10 to about 20 carbon atoms. The fatty acids used in making the soaps can be obtained from natural sources such as, for instance, plant or animal-derived glycerides (e.g., palm oil, coconut oil, soybean oil, castor oil, tallow, lard, etc.) The fatty acids can also be synthetically prepared. Soaps are described in more detail in U.S. Patent No. 4,557,853, cited above.

Amphoteric and zwitterionic surfactants are also useful herein. Examples of amphoteric and zwitterionic surfactants which can be used in the compositions of the present invention are those which are broadly described as derivatives of aliphatic secondary and tertiary amines in which the aliphatic radical can be straight or branched chain and wherein one of the aliphatic substituents contains from about 8 to about 22 carbon atoms (preferably C<sub>8</sub> - C<sub>18</sub>) and one contains an anionic water solubilizing group, e.g., carboxy, sulfonate, sulfate, phosphate, or phosphonate. Examples are alkyl imino acetates, and iminodialkanoates and aminoalkanoates of the formulas  $RN(CH_2)_mCO_2M]_2$  and  $RNH(CH_2)_mCO_2M$  wherein m is from 1 to 4, R is a C<sub>8</sub>-C<sub>22</sub> alkyl or alkenyl, and M is H, alkali metal, alkaline earth metal, ammonium, or alkanolammonium. Also included are imidazolinium and ammonium derivatives. Specific examples of suitable amphoteric surfactants include sodium 3-dodecyl-aminopropionate, sodium 3-dodecylaminopropane sulfonate, N-alkyltaurines such as the one prepared by reacting dodecylamine with sodium isethionate according to the teaching of U.S. Patent 2,658,072 which is incorporated herein by reference in its entirety; N<sup>-</sup>higher alkyl aspartic acids such as those produced according to the teaching of U.S. Patent 2,438,091 which is incorporated herein by reference in its entirety; and the products sold under the trade name "Miranol" and described in U.S. Patent 2,528,378, which is incorporated herein by reference in its entirety. Other examples of useful amphoteric surfactants include phosphates, such as coamidopropyl PG-dimonium chloride phosphate (commercially available as Monaquat PTC, from Mona Corp.).

Also useful herein as amphoteric or zwitterionic surfactants are the betaines. Examples of betaines include the higher alkyl betaines, such as coco dimethyl carboxymethyl betaine, lauryl dimethyl carboxymethyl betaine, lauryl dimethyl alphacarboxyethyl betaine, cetyl dimethyl carboxymethyl betaine, cetyl dimethyl betaine (available as Lonzaine 16SP from Lonza Corp.), lauryl bis-(2-hydroxyethyl) carboxymethyl betaine, stearyl bis-(2-hydroxypropyl) carboxymethyl betaine, oleyl dimethyl gamma-carboxypropyl betaine, lauryl bis-(2-hydroxypropyl)alpha-carboxyethyl betaine, coco dimethyl sulfopropyl betaine, stearyl dimethyl sulfopropyl betaine, lauryl dimethyl sulfoethyl betaine, lauryl bis-(2-hydroxyethyl) sulfopropyl betaine, and amidobetaines and amidosulfobetaines (wherein the  $RCONH(CH_2)_3$  radical is attached to the nitrogen atom of the betaine), oleyl betaine (available as amphoteric Velvetex OLB-50 from Henkel), and cocamidopropyl betaine (available as Velvetex BK-35 and BA-35 from Henkel).

Other useful amphoteric and zwitterionic surfactants include the sultaines and hydroxysultaines such as cocamidopropyl hydroxysultaine (available as Mirataine CBS from Rhone-Poulenc), and the alkanoyl sarcosinates corresponding to the formula  $RCON(CH_3)CH_2CH_2CO_2M$  wherein R is alkyl or alkenyl of about 10 to about 20 carbon atoms, and M is a water-soluble cation such as ammonium, sodium, potassium and



trialkanolamine (e.g., triethanolamine), a preferred example of which is sodium lauroyl sarcosinate.

(iii) Water

The preferred oil-in-water emulsion comprises from about 25% to about 98%, preferably from about 65% to about 95%, more preferably from about 70% to about 90% water by weight of the carrier.

The hydrophobic phase is dispersed in the continuous aqueous phase. The hydrophobic phase may contain water insoluble or partially soluble materials such as are known in the art, including but not limited to the silicones described herein in reference to silicone-in-water emulsions, and other oils and lipids used as emollients. Preferred oil-in-water emulsions contain an emollient.

**b) Water-in-silicone emulsion**

Water-in-silicone emulsions contain a continuous silicone phase and a dispersed aqueous phase. As will be understood by those skilled in the art, the tocopherol sorbate distributes primarily into the silicone phase. Other materials such as described herein may also be incorporated into one or both of these phases and distribute primarily in a given phase depending on their solubility or dispersibility in that phase. For example, water soluble or dispersible materials tend to distribute in the aqueous phase; oil soluble or dispersible materials tend to distribute in the silicone phase.

(i) Continuous silicone phase

Preferred water-in-silicone emulsions of the present invention comprise from about 1% to about 60%, preferably from about 5% to about 40%, more preferably from about 10% to about 20%, by weight of a continuous silicone phase. The continuous silicone phase exists as an external phase that contains or surrounds the discontinuous aqueous phase described hereinafter. The continuous silicone phase contains a polyorganosiloxane oil.

A preferred water-in-silicone emulsion system is formulated to provide an oxidatively stable vehicle for the retinoid, when employed. The continuous silicone phase of these preferred emulsions comprises between about 50% and about 99.9% by weight of organopolysiloxane oil and less than about 50% by weight of a non-silicone oil. In an especially preferred embodiment, the continuous silicone phase comprises at least about 50%, preferably from about 60% to about 99.9%, more preferably from about 70% to about 99.9%, and even more preferably from about 80% to about 99.9%, polyorganosiloxane oil by weight of the continuous silicone phase, and up to about 50% non-silicone oils, preferably less than about 40%, more preferably less than about 30%, even more preferably less than about 10%, and most preferably less than about 2%, by weight of the continuous silicone phase. These preferred emulsion systems provide more oxidative stability to the retinoid over extended periods of time than comparable water-in-oil emulsions

containing lower concentrations of the polyorganosiloxane oil. Concentrations of non-silicone oils in the continuous silicone phase are minimized or avoided altogether so as to further enhance oxidative stability of the selected retinoid in the compositions. Water-in-silicone emulsions of this type are described in copending U.S. Patent Application Serial No. 08/570,275, filed December 11, 1995, in the names of Joseph Michael Zukowski, Brent William Mason, Larry Richard Robinson and Greg George Hillebrand, incorporated herein by reference.

The organopolysiloxane oil for use in the composition may be volatile, non-volatile, or a mixture of volatile and non-volatile silicones. The term "nonvolatile" as used in this context refers to those silicones that are liquid under ambient conditions and have a flash point (under one atmospheric of pressure) of or greater than about 100°C. The term "volatile" as used in this context refers to all other silicone oils. Suitable organopolysiloxanes can be selected from a wide variety of silicones spanning a broad range of volatilities and viscosities. Examples of suitable organopolysiloxane oils include polyalkylsiloxanes, cyclic polyalkylsiloxanes, and polyalkylarylsiloxanes.

Polyalkylsiloxanes useful in the composition herein include polyalkylsiloxanes with viscosities of from about 0.5 to about 1,000,000 centistokes at 25°C. Such polyalkylsiloxanes can be represented by the general chemical formula  $R_3SiO[R_2SiO]_xSiR_3$  wherein R is an alkyl group having from one to about 30 carbon atoms (preferably R is methyl or ethyl, more preferably methyl; also mixed alkyl groups can be used in the same molecule), and x is an integer from 0 to about 10,000, chosen to achieve the desired molecular weight which can range to over about 10,000,000. Commercially available polyalkylsiloxanes include the polydimethylsiloxanes, which are also known as dimethicones, examples of which include the Vicasil® series sold by General Electric Company and the Dow Corning® 200 series sold by Dow Corning Corporation. Specific examples of suitable polydimethylsiloxanes include Dow Corning® 200 fluid having a viscosity of 0.65 centistokes and a boiling point of 100°C, Dow Corning® 225 fluid having a viscosity of 10 centistokes and a boiling point greater than 200°C, and Dow Corning® 200 fluids having viscosities of 50, 350, and 12,500 centistokes, respectively, and boiling points greater than 200°C. Suitable dimethicones include those represented by the chemical formula  $(CH_3)_3SiO[(CH_3)_2SiO]_x[CH_3RSiO]_ySi(CH_3)_3$  wherein R is straight or branched chain alkyl having from two to about 30 carbon atoms and x and y are each integers of 1 or greater selected to achieve the desired molecular weight which can range to over about 10,000,000. Examples of these alkyl-substituted dimethicones include cetyl dimethicone and lauryl dimethicone.

Cyclic polyalkylsiloxanes suitable for use in the composition include those represented by the chemical formula  $[SiR_2-O]_n$  wherein R is an alkyl group (preferably R is methyl or ethyl, more preferably methyl) and n is an integer from about 3 to about 8, more preferably n is an

integer from about 3 to about 7, and most preferably  $n$  is an integer from about 4 to about 6. When  $R$  is methyl, these materials are typically referred to as cyclomethicones. Commercially available cyclomethicones include Dow Corning® 244 fluid having a viscosity of 2.5 centistokes, and a boiling point of 172°C, which primarily contains the cyclomethicone tetramer (i.e.  $n=4$ ), Dow Corning® 344 fluid having a viscosity of 2.5 centistokes and a boiling point of 178°C, which primarily contains the cyclomethicone pentamer (i.e.  $n=5$ ), Dow Corning® 245 fluid having a viscosity of 4.2 centistokes and a boiling point of 205°C, which primarily contains a mixture of the cyclomethicone tetramer and pentamer (i.e.  $n=4$  and 5), and Dow Corning® 345 fluid having a viscosity of 4.5 centistokes and a boiling point of 217°, which primarily contains a mixture of the cyclomethicone tetramer, pentamer, and hexamer (i.e.  $n=4$ , 5, and 6).

Also useful are materials such as trimethylsiloxysilicate, which is a polymeric material corresponding to the general chemical formula  $[(CH_3)_3SiO_{1/2}]_x[SiO_2]_y$ , wherein  $x$  is an integer from about 1 to about 500 and  $y$  is an integer from about 1 to about 500. A commercially available trimethylsiloxysilicate is sold as a mixture with dimethicone as Dow Corning® 593 fluid.

Dimethiconols are also suitable for use in the composition. These compounds can be represented by the chemical formulas  $R_3SiO[R_2SiO]_xSiR_2OH$  and  $HOR_2SiO[R_2SiO]_xSiR_2OH$  wherein  $R$  is an alkyl group (preferably  $R$  is methyl or ethyl, more preferably methyl) and  $x$  is an integer from 0 to about 500, chosen to achieve the desired molecular weight. Commercially available dimethiconols are typically sold as mixtures with dimethicone or cyclomethicone (e.g. Dow Corning® 1401, 1402, and 1403 fluids).

Polyalkylaryl siloxanes are also suitable for use in the composition. Polymethylphenyl siloxanes having viscosities from about 15 to about 65 centistokes at 25°C are especially useful.

Preferred for use herein are organopolysiloxanes selected from the group consisting of polyalkylsiloxanes, alkyl substituted dimethicones, cyclomethicones, trimethylsiloxysilicates, dimethiconols, polyalkylaryl siloxanes, and mixtures thereof. More preferred for use herein are polyalkylsiloxanes and cyclomethicones. Preferred among the polyalkylsiloxanes are dimethicones.

As stated above, the continuous silicone phase may contain one or more non-silicone oils. When the compositions contain a retinoid, concentrations of non-silicone oils in the continuous silicone phase are preferably minimized or avoided altogether so as to further enhance oxidative stability of the selected retinoid. Suitable non-silicone oils have a melting point of about 25°C or less under about one atmosphere of pressure. Examples of non-silicone oils suitable for use in the continuous silicone phase are those well known in the chemical arts in

topical personal care products in the form of water-in-oil emulsions, e.g., mineral oil, vegetable oils, synthetic oils, semisynthetic oils, etc..

(ii) Dispersed aqueous phase

The water-in-silicone emulsions of the present invention comprise from about 30% to about 90%, more preferably from about 50% to about 85%, and most preferably from about 70% to about 80% of a dispersed aqueous phase. The dispersed aqueous phase is a dispersion of small aqueous particles or droplets suspended in and surrounded by the continuous silicone phase described hereinbefore.

The aqueous phase can be water, or a combination of water and one or more water soluble or dispersible ingredients. Nonlimiting examples of such optional ingredients include thickeners, acids, bases, salts, chelants, gums, water-soluble or dispersible alcohols and polyols, buffers, preservatives, sunscreens agents, colorings, and the like.

The topical compositions of the present invention will typically comprise from about 25% to about 90%, preferably from about 40% to about 80%, more preferably from about 60% to about 80%, water in the dispersed aqueous phase by weight of the composition.

(iii) Emulsifier for dispersing the aqueous phase

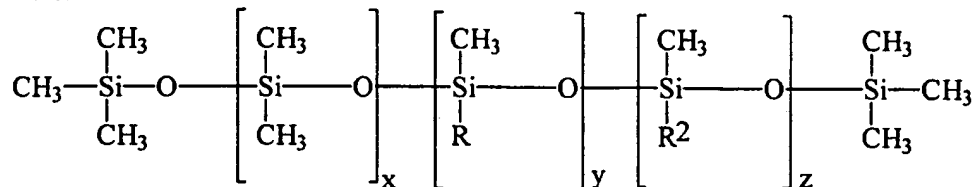
The water-in-silicone emulsions of the present invention preferably comprise an emulsifier. In a preferred embodiment, the composition contains from about 0.1% to about 10% emulsifier, more preferably from about 0.5% to about 7.5%, most preferably from about 1% to about 5%, emulsifier by weight of the composition. The emulsifier helps disperse and suspend the aqueous phase within the continuous silicone phase.

A wide variety of emulsifying agents can be employed herein to form the preferred water-in-silicone emulsion. Known or conventional emulsifying agents can be used in the composition, provided that the selected emulsifying agent is chemically and physically compatible with essential components of the composition, and provides the desired dispersion characteristics. Suitable emulsifiers include silicone emulsifiers, non-silicon-containing emulsifiers, and mixtures thereof, known by those skilled in the art for use in topical personal care products. Preferably these emulsifiers have an HLB value of or less than about 14, more preferably from about 2 to about 14, and most preferably from about 4 to about 14. Emulsifiers having an HLB value outside of these ranges can be used in combination with other emulsifiers to achieve an effective weighted average HLB for the combination that falls within these ranges.

Silicone emulsifiers are preferred. A wide variety of silicone emulsifiers are useful herein. These silicone emulsifiers are typically organically modified organopolysiloxanes, also known to those skilled in the art as silicone surfactants. Useful silicone emulsifiers include dimethicone copolyols. These materials are polydimethyl siloxanes which have been modified to include polyether side chains such as polyethylene oxide chains, polypropylene oxide chains,

mixtures of these chains, and polyether chains containing moieties derived from both ethylene oxide and propylene oxide. Other examples include alkyl-modified dimethicone copolyols, i.e., compounds which contain C2-C30 pendant side chains. Still other useful dimethicone copolyols include materials having various cationic, anionic, amphoteric, and zwitterionic pendant moieties.

The dimethicone copolyol emulsifiers useful herein can be described by the following general structure:



wherein R is C1-C30 straight, branched, or cyclic alkyl and R<sup>2</sup> is selected from the group consisting of

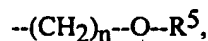


and



wherein n is an integer from 3 to about 10; R<sup>3</sup> and R<sup>4</sup> are selected from the group consisting of H and C1-C6 straight or branched chain alkyl such that R<sup>3</sup> and R<sup>4</sup> are not simultaneously the same; and m, o, x, and y are selected such that the molecule has an overall molecular weight from about 200 to about 10,000,000, with m, o, x, and y being independently selected from integers of zero or greater such that m and o are not both simultaneously zero, and z being independently selected from integers of 1 or greater. It is recognized that positional isomers of these copolyols can be achieved. The chemical representations depicted above for the R<sup>2</sup> moieties containing the R<sup>3</sup> and R<sup>4</sup> groups are not meant to be limiting but are shown as such for convenience.

Also useful herein, although not strictly classified as dimethicone copolyols, are silicone surfactants as depicted in the structures in the previous paragraph wherein R<sup>2</sup> is:



wherein R<sup>5</sup> is a cationic, anionic, amphoteric, or zwitterionic moiety.

Nonlimiting examples of dimethicone copolyols and other silicone surfactants useful as emulsifiers herein include polydimethylsiloxane polyether copolymers with pendant polyethylene oxide sidechains, polydimethylsiloxane polyether copolymers with pendant polypropylene oxide sidechains, polydimethylsiloxane polyether copolymers with pendant mixed polyethylene oxide and polypropylene oxide sidechains, polydimethylsiloxane polyether copolymers with pendant mixed poly(ethylene)(propylene)oxide sidechains, polydimethylsiloxane polyether copolymers with pendant organobetaine sidechains,

polydimethylsiloxane polyether copolymers with pendant carboxylate sidechains, polydimethylsiloxane polyether copolymers with pendant quaternary ammonium sidechains; and also further modifications of the preceding copolymers containing pendant C2-C30 straight, branched, or cyclic alkyl moieties. Examples of commercially available dimethicone copolyols useful herein sold by Dow Corning Corporation are Dow Corning® 190, 193, Q2-5220, 2501 Wax, 2-5324 fluid, and 3225C (this latter material being sold as a mixture with cyclomethicone). Cetyl dimethicone copolyol is commercially available as a mixture with polyglyceryl-4 isostearate (and) hexyl laurate and is sold under the tradename ABIL® WE-09 (available from Goldschmidt). Cetyl dimethicone copolyol is also commercially available as a mixture with hexyl laurate (and) polyglyceryl-3 oleate (and) cetyl dimethicone and is sold under the tradename ABIL® WS-08 (also available from Goldschmidt). Other nonlimiting examples of dimethicone copolyols also include lauryl dimethicone copolyol, dimethicone copolyol acetate, dimethicone copolyol adipate, dimethicone copolyolamine, dimethicone copolyol behenate, dimethicone copolyol butyl ether, dimethicone copolyol hydroxy stearate, dimethicone copolyol isostearate, dimethicone copolyol laurate, dimethicone copolyol methyl ether, dimethicone copolyol phosphate, and dimethicone copolyol stearate. See International Cosmetic Ingredient Dictionary, Fifth Edition, 1993, which is incorporated by reference herein in its entirety.

Dimethicone copolyol emulsifiers useful herein are described, for example, in U.S. Patent No. 4,960,764, to Figueroa, Jr. et al., issued October 2, 1990; European Patent No. EP 330,369, to SanoGueira, published August 30, 1989; G.H. Dahms, et al., "New Formulation Possibilities Offered by Silicone Copolyols," Cosmetics & Toiletries, vol. 110, pp. 91-100, March 1995; M.E. Carlotti et al., "Optimization of W/O-S Emulsions And Study Of The Quantitative Relationships Between Ester Structure And Emulsion Properties," J. Dispersion Science And Technology, 13(3), 315-336 (1992); P. Hameyer, "Comparative Technological Investigations of Organic and Organosilicone Emulsifiers in Cosmetic Water-in-Oil Emulsion Preparations," HAPPI 28(4), pp. 88-128 (1991); J. Smid-Korbar et al., "Efficiency and usability of silicone surfactants in emulsions," Provisional Communication, International Journal of Cosmetic Science, 12, 135-139 (1990); and D.G. Krzysik et al., "A New Silicone Emulsifier For Water-in-Oil Systems," Drug and Cosmetic Industry, vol. 146(4) pp. 28-81 (April 1990); incorporated by reference herein in their entirety.

Among the non-silicon-containing emulsifiers useful herein are various non-ionic and anionic emulsifying agents such as sugar esters and polyesters, alkoxylated sugar esters and polyesters, C1-C30 fatty acid esters of C1-C30 fatty alcohols, alkoxylated derivatives of C1-C30 fatty acid esters of C1-C30 fatty alcohols, alkoxylated ethers of C1-C30 fatty alcohols, polyglyceryl esters of C1-C30 fatty acids, C1-C30 esters of polyols, C1-C30 ethers of polyols.

alkyl phosphates, polyoxyalkylene fatty ether phosphates, fatty acid amides, acyl lactylates, soaps, and mixtures thereof. Other suitable emulsifiers are described, for example, in McCutcheon's, Detergents and Emulsifiers, North American Edition (1986), published by Allured Publishing Corporation; U.S. Patent No. 5,011,681 to Ciotti et al., issued April 30, 1991; U.S. Patent No. 4,421,769 to Dixon et al., issued December 20, 1983; and U.S. Patent No. 3,755,560 to Dickert et al., issued August 28, 1973; these references are incorporated herein by reference in their entirety.

Nonlimiting examples of these non-silicone-containing emulsifiers include: polyethylene glycol 20 sorbitan monolaurate (Polysorbate 20), polyethylene glycol 5 soya sterol, Steareth-20, Cetareth-20, PPG-2 methyl glucose ether distearate, Ceteth-10, Polysorbate 80, cetyl phosphate, potassium cetyl phosphate, diethanolamine cetyl phosphate, Polysorbate 60, glyceryl stearate, PEG-100 stearate, polyoxyethylene 20 sorbitan trioleate (Polysorbate 85), sorbitan monolaurate, polyoxyethylene 4 lauryl ether sodium stearate, polyglyceryl-4 isostearate, hexyl laurate, and mixtures thereof.

The topical compositions of the subject invention, including but not limited to lotions and creams, may comprise a dermatologically acceptable emollient. Such compositions preferably contain from about 2% to about 50% of the emollient. As used herein, "emollient" refers to a material used for the prevention or relief of dryness, as well as for the protection of the skin. A wide variety of suitable emollients are known and may be used herein. Sagarin, Cosmetics, Science and Technology, 2nd Edition, Vol. 1, pp. 32-43 (1972), incorporated herein by reference, contains numerous examples of materials suitable as an emollient.

Lotions and creams according to the present invention generally comprise a solution carrier system and one or more emollients. Lotions typically comprise from about 1% to about 20%, preferably from about 5% to about 10%, of emollient; and from about 50% to about 90%, preferably from about 60% to about 80%, water. A cream typically comprises from about 5% to about 50%, preferably from about 10% to about 20%, of emollient; and from about 45% to about 85%, preferably from about 50% to about 75%, water.

Ointments of the present invention may comprise a simple carrier base of animal or vegetable oils or semi-solid hydrocarbons (oleaginous); absorption ointment bases which absorb water to form emulsions; or water soluble carriers, e.g., a water soluble solution carrier. Ointments may further comprise a thickening agent, such as described in Sagarin, Cosmetics, Science and Technology, 2nd Edition, Vol. 1, pp. 72-73 (1972), incorporated herein by reference, and/or an emollient. For example, an ointment may comprise from about 2% to about 10% of an emollient; and from about 0.1% to about 4% of a thickening agent.

Compositions of this invention useful for cleansing the skin or hair ("cleansers") are formulated with a suitable carrier, e.g., as described above, and preferably contain, in addition to

tocopherol sorbate, from about 1% to about 90%, more preferably from about 5% to about 10%, of a dermatologically acceptable surfactant. The surfactant is suitably selected from anionic, nonionic, zwitterionic, amphoteric and ampholytic surfactants, as well as mixtures of these surfactants. Such surfactants are well known to those skilled in the detergency art. Nonlimiting examples of possible surfactants include isoceteth-20, sodium methyl cocoyl taurate, sodium methyl oleoyl taurate, and sodium lauryl sulfate. See U.S. Patent No. 4,800,197, to Kowcz et al., issued January 24, 1989, which is incorporated herein by reference in its entirety, for exemplary surfactants useful herein. Examples of a broad variety of additional surfactants useful herein are described in McCutcheon's Detergents and Emulsifiers, North American Edition (1986), published by Allured Publishing Corporation, which is incorporated herein by reference in its entirety. The cleansing compositions can optionally contain, at their art-established levels, other materials which are conventionally used in cleansing compositions.

The physical form of the cleansing compositions is not critical. The compositions can be, for example, formulated as toilet bars, liquids, shampoos, bath gels, hair conditioners, hair tonics, pastes, or mousses. Toilet bars are most preferred since this is the form of cleansing agent most commonly used to wash the skin. Rinse-off cleansing compositions, such as shampoos, require a delivery system adequate to deposit sufficient levels of actives on the skin and scalp. A preferred delivery system involves the use of insoluble complexes. For a more complete disclosure of such delivery systems, see U.S. Patent 4,835,148, Barford et al., issued May 30, 1989, incorporated herein by reference in its entirety.

As used herein, the term "foundation" refers to a liquid, semi-liquid, semi-solid, or solid skin cosmetic which includes, but is not limited to, lotions, creams, gels, pastes, cakes, and the like. Typically the foundation is used over a large area of the skin, such as over the face, to provide a particular look. Foundations are typically used to provide an adherent base for color cosmetics such as rouge, blusher, powder and the like, and tend to hide skin imperfections and impart a smooth, even appearance to the skin. Foundations of the present invention include a dermatologically acceptable carrier for the tocopherol sorbate and optional other actives, and may include conventional ingredients such as oils, colorants, pigments, emollients, fragrances, waxes, stabilizers, and the like. Exemplary carriers and such other ingredients which are suitable for use herein are described, for example, in copending patent application Serial No. 08/430,961, filed on April 28, 1995, in the names of Marcia L. Canter, Brian D. Barford, and Brian D. Hofrichter, incorporated herein by reference.

The compositions of the present invention are preferably formulated to have a pH of or below about 10.5. The pH values of these compositions preferably range from or about 2 to or about 10.5, more preferably from or about 3 to or about 8, even more preferably from or about 4 to or about 7.



### Optional Components

The topical compositions of the present invention may comprise a wide variety of optional components, provided that such optional components are physically and chemically compatible with the essential components described herein, and do not unduly impair stability, efficacy or other use benefits associated with the compositions of the present invention. Any optional ingredients should be compatible with the tocopherol sorbate such that its activity does not decrease unacceptably, preferably not to any significant extent, over a useful period (preferably at least about two years under normal storage conditions). Optional components may be dispersed, dissolved or the like in the carrier of the present compositions.

Optional components include aesthetic agents and other active agents. For example, the compositions may include absorbents, abrasives, anticaking agents, antifoaming agents, antimicrobial agents, binders, biological additives, buffering agents, bulking agents, chemical additives, cosmetic biocides, denaturants, cosmetic astringents, drug astringents, external analgesics, film formers, humectants, opacifying agents, fragrances, pigments, colorings, essential oils, skin sensates, emollients, occlusive agents, skin soothing agents, skin healing agents, pH adjusters, plasticizers, preservatives, preservative enhancers, propellants, reducing agents, skin-conditioning agents, skin penetration enhancing agents, skin protectants, solvents, suspending agents, emulsifiers, thickening agents, solubilizing agents, sunscreens, sunblocks, ultraviolet light absorbers or scattering agents, sunless tanning agents, antioxidants and/or radical scavengers, chelating agents, sequestrants, anti-acne agents, anti-inflammatory agents, anti-androgens, depilation agents, desquamation agents/exfoliants/keratolytics, organic hydroxy acids, vitamins and derivatives thereof, and natural extracts. Such other materials are known in the art. For example, nonexclusive examples of such materials are described in Harry's Cosmetology, 7th Ed., Harry & Wilkinson (Hill Publishers, London 1982); in Pharmaceutical Dosage Forms- Disperse Systems; Lieberman, Rieger & Banker, Vols. 1 (1988) & 2 (1989); Marcel Decker, Inc.; in The Chemistry and Manufacture of Cosmetics, 2nd. Ed., deNavarre (Van Nostrand 1962-1965); and in The Handbook of Cosmetic Science and Technology, 1st Ed., Knowlton & Pearce (Elsevier 1993).

Specific examples of optional components include the following. It is to be understood that notwithstanding a particular classification, a compound may have other utilities including those described herein.

#### A. Anti-Inflammatory Agents

Preferred compositions of the present invention include a safe and effective amount of an anti-inflammatory, preferably from or about 0.1% to or about 10%, more preferably from or about 0.5% to or about 5%, of the composition. The anti-inflammatory agent enhances the skin appearance benefits of the present invention, e.g., such agents contribute to a more uniform and

acceptable skin color, e.g., by treating diffuse and more localized redness due to inflammation, sunburn, etc. The exact amount of anti-inflammatory agent to be used in the compositions will depend on the particular anti-inflammatory agent utilized since such agents vary widely in potency.

Steroidal anti-inflammatory agents, including but not limited to, corticosteroids such as hydrocortisone, hydroxyltriamcinolone, alpha-methyl dexamethasone, dexamethasone-phosphate, beclomethasone dipropionates, clobetasol valerate, desonide, desoxymethasone, desoxycorticosterone acetate, dexamethasone, dichlorisone, diflorasone diacetate, difluocortolone valerate, fluadrenolone, fluclorolone acetonide, fludrocortisone, flumethasone pivalate, fluosinolone acetonide, fluocinonide, flucortine butylesters, fluocortolone, fluprednidene (fluprednylidene) acetate, flurandrenolone, halcinonide, hydrocortisone acetate, hydrocortisone butyrate, methylprednisolone, triamcinolone acetonide, cortisone, cortodoxone, flucetonide, fludrocortisone, difluorosone diacetate, fluradrenolone, fludrocortisone, difluorosone diacetate, fluradrenolone acetonide, medrysone, amcinafel, amcinafide, betamethasone and the balance of its esters, chloroprednisone, chlorprednisone acetate, clocortelone, clescinalone, dichlorisone, diflurprednate, flucloronide, flunisolid, fluoromethalone, fluperolone, fluprednisolone, hydrocortisone valerate, hydrocortisone cyclopentylpropionate, hydrocortamate, meprednisone, paramethasone, prednisolone, prednisone, beclomethasone dipropionate, triamcinolone, and mixtures thereof may be used. The preferred steroidal anti-inflammatory for use is hydrocortisone.

A second class of anti-inflammatory agents which is useful in the compositions includes the nonsteroidal anti-inflammatory agents. The variety of compounds encompassed by this group are well-known to those skilled in the art. For detailed disclosure of the chemical structure, synthesis, side effects, etc. of non-steroidal anti-inflammatory agents, reference may be had to standard texts, including Anti-inflammatory and Anti-Rheumatic Drugs, K.D. Rainsford, Vol. I-III, CRC Press, Boca Raton, (1985), and Anti-inflammatory Agents, Chemistry and Pharmacology, 1, R.A. Scherrer, et al., Academic Press, New York (1974), each incorporated herein by reference.

Specific non-steroidal anti-inflammatory agents useful in the compositions of the invention include, but are not limited to:

- 1) the oxicams, such as piroxicam, isoxicam, tenoxicam, sudoxicam, and CP-14,304;
- 2) the salicylates, such as aspirin, disalcid, benorylate, trilisate, safapryn, solprin, diflunisal, and fendosal;

3) the acetic acid derivatives, such as diclofenac, fenclofenac, indomethacin, sulindac, tolmetin, isoxepac, furofenac, tiopinac, zidometacin, acematacin, fentiazac, zomepirac, clindanac, oxepinac, felbinac, and ketorolac;

4) the fenamates, such as mefenamic, meclofenamic, flufenamic, niflumic, and tolfenamic acids;

5) the propionic acid derivatives, such as ibuprofen, naproxen, benoxaprofen, flurbiprofen, ketoprofen, fenoprofen, fenbufen, indoprofen, pirofen, carprofen, oxaprozin, pranoprofen, miroprofen, tiroxaprofen, suprofen, alminoprofen, and tiaprofenic; and

6) the pyrazoles, such as phenylbutazone, oxyphenbutazone, feprazone, azapropazone, and trimethazone.

Mixtures of these non-steroidal anti-inflammatory agents may also be employed, as well as the dermatologically acceptable salts and esters of these agents. For example, etofenamate, a flufenamic acid derivative, is particularly useful for topical application. Of the nonsteroidal anti-inflammatory agents, ibuprofen, naproxen, flufenamic acid, etofenamate, aspirin, mefenamic acid, meclofenamic acid, piroxicam and felbinac are preferred; ibuprofen, naproxen, aspirin, etofenamate, and flufenamic acid are most preferred.

Finally, so-called "natural" anti-inflammatory agents are useful in the subject invention. For example, candelilla wax, bisabolol (e.g., alpha bisabolol), aloe vera, Manjistha (Rubia, particularly Rubia Cordifolia), Guggal (Commiphora, particularly Commiphora Mukul), kola extract, chamomile extract (Matricaria chamomilla), sea whip extract, Yarrow (Achillea millifolium), Gardenia (Gardenia jasminoides), Horse Chestnut (Aesculus hippocastanum), Japanese Angelica (Angelica acutiloba), Jujube (Ziziphus jujuba), Loquat leaf (Eriobotrya japonica), Mouton Bark (Paeonia suffruticosa), Mugwort (Artemisia princeps), Mulberry leaf (Morus bombycis), Peach leaf (Prunus persicus), Peony root (Paeonia albiflora), Phellodendron (Phellodendron amurense), Pine cone (Pinus sylvestrus), Platycodon (Platycodon grandiflorum), Safflower (Carthamus tinctorius), Sage (Salvia officinalis), Sasa veitchii (Sasa veitchii), Saxifrage (Saxifraga stolonifera), Scutellaria (Scutellaria baicalensis), Shikonine (Lithospermum erythrorhizon), Tilia (Tilia sylvestrus), White Lily (Lilium candidum), Soporina (Sophora flavescens), and Sambucus (Sambucus nigra) may be used (as applicable, the foregoing plant genus/species names indicate that the compound may be derived from that genus/species). Suitable extracts of these types are commercially available from a number of sources, e.g., International Sourcing, Inc. (UpperSaddle River, NJ), and Maruzen Pharmaceuticals Co. LTD. (Hiroshima, Japan)

Additional anti-inflammatory agents useful herein include compounds of the Licorice (the plant genus/species Glycyrrhiza glabra) family, including glycyrrhetic acid, glycyrrhizic acid, and derivatives thereof (e.g., salts and esters). Suitable salts of the foregoing compounds

include metal and ammonium salts. Suitable esters include C<sub>2</sub> - C<sub>24</sub> saturated or unsaturated esters of the acids, preferably C<sub>10</sub> - C<sub>24</sub>, more preferably C<sub>16</sub> - C<sub>24</sub>. Specific examples of the foregoing include oil soluble licorice extract, the glycyrrhizic and glycyrrhetic acids themselves, Monoammonium Glycyrrhizinate, Monopotassium Glycyrrhizinate, Dipotassium Glycyrrhizinate, 1--beta-Glycyrrhetic acid, Stearyl Glycyrrhetinate, and 3-stearyloxy-Glycyrrhetinic acid, and disodium 3-succinyloxy-beta-glycyrrhetinate. Stearyl Glycyrrhetinate is preferred.

**B. Anti-Oxidants/Radical Scavengers**

Preferred compositions of the subject invention include an anti-oxidant/radical scavenger. The anti-oxidant/radical scavenger is especially useful for providing protection against UV radiation which can cause increased scaling or texture changes in the stratum corneum and against other environmental agents which can cause skin damage. Such compounds may also may enhance the skin lightening benefits of the present compositions, e.g., by influencing biological oxidative processes.

A safe and effective amount of an anti-oxidant/radical scavenger may be added to the compositions of the subject invention, preferably from or about 0.1% to or about 10%, more preferably from or about 1% to or about 5%, e.g., about 3%, of the composition.

Exemplary anti-oxidants/radical scavengers include ascorbic acid (vitamin C) and derivatives thereof (e.g., salts, esters thereof, including C<sub>2</sub> - C<sub>24</sub> saturated or unsaturated esters, mono-, di- and tri- valent metal phosphates, sulfates and carbonates, and such salts of the esters); other tocopherol compounds, including tocopherol (vitamin E) and other esters of tocopherol, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (commercially available under the tradename Trolox<sup>R</sup>); tocopheryl retinoate, butylated hydroxy benzenes (e.g. butylated hydroxy toluene (BHT) and butylated hydroxy anisole (BHA)); butylated hydroxy benzoates (BHB) and their salts; gallic acid and its alkyl esters, especially propyl gallate; uric acid and its salts and alkyl esters, sorbic acid and its salts; amines (e.g., N,N-diethylhydroxylamine, amino-guanidine); dihydroxy fumaric acid and its salts; lysine pidolate; arginine pilolate; nordihydroguaiaretic acid; bioflavonoids; amino acids such as lysine, methionine and proline; superoxide dismutase; silymarin; tea extracts (especially green tea extracts); grape skin/seed extracts; melanin; rosemary sulfites; erythorbic acid; and Licorice extracts. Other anti-oxidant/radical scavengers include redox sensitive polypeptides such as thioredoxin, glutaredoxin, and protein disulfide isomerase.

Preferred anti-oxidants/radical scavengers are selected from ascorbic acid (vitamin C) and its derivatives, specific examples being magnesium ascorbyl phosphate, sodium ascorbyl phosphate, potassium ascorbyl phosphate, calcium ascorbyl phosphate, aluminum ascorbyl phosphate, magnesium ascorbyl sulfate, potassium ascorbyl sulfate, aluminum ascorbyl sulfate,

inositol ascorbate, sodium benzilidene ascorbate, L-3-ethyl ascorbic acid, galctylpyranosyl-L-ascorbic acid, ascorbate phospholipid, zinc ascorbate, 2,5,6, tri-o-pivaloylascorbate monopivaloyl ascorbate, and ascorbyl carbonates. Metal phosphates, sulfates and carbonates, and mono-, di- and tri-valent salts (e.g., Group I/II metal salts) of the above-described ascorbate esters are preferred, with the metal phosphates being more preferred and magnesium ascorbyl phosphate being most preferred.

C. Retinoids

Preferred compositions of the present invention contain a safe and effective amount of a retinoid. The retinoid enhances the skin appearance benefits of the present invention. For example, the retinoid may prevent pigment accumulation within the more rapidly dividing and migrating keratinocytes, and enhance the pigment-reducing ability of skin lightening agents. The retinoid also helps diminish fine lines, wrinkles, or other textural discontinuities of the skin.

As used herein, "retinoid" means all natural and/or synthetic analogs of vitamin A or retinol-like compounds which possess the biological activity of vitamin A or vitamin A acid in the skin as well as the geometric isomers and stereoisomers of these compounds. The retinoid is preferably retinol, retinol esters (e.g., C<sub>2</sub> - C<sub>22</sub> alkyl esters of retinol, including retinyl palmitate, retinyl acetate, retinyl propionate), retinal, retinoic acid (including all-trans retinoic acid and/or 13-cis-retinoic acid), and/or other retinoic acid esters. These compounds are well known in the art and are commercially available from a number of sources, e.g., Sigma Chemical Company (St. Louis, MO), Hoffmann LaRoche (Nutley, New Jersey) and Boehringer Mannheim (Indianapolis, IN). Other retinoids which are useful herein are described in U.S. Patent Nos. 4,677,120, issued Jun. 30, 1987 to Parish et al.; 4,885,311, issued Dec. 5, 1989 to Parish et al.; 5,049,584, issued Sep. 17, 1991 to Purcell et al.; 5,124,356, issued Jun. 23, 1992 to Purcell et al.; and Reissue 34,075, issued Sep. 22, 1992 to Purcell et al.. Other suitable retinoids are tocopheryl-retinoate [tocopherol ester of retinoic acid (trans- or cis-)], adapalene {6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthoic acid}, and tazarotene (ethyl 6-[2-(4,4-dimethylthiochroman-6-yl)-ethynyl]nicotinate). One or more retinoids may be used herein. Preferred retinoids are retinol, retinyl palmitate, retinyl acetate, retinyl propionate, retinal and combinations thereof. More preferred are retinol and retinyl propionate.

The retinoid is generally added in an amount of from or about 0.005% to or about 2%, more preferably from or about 0.01% to or about 2%. Retinol is most preferably used in an amount of from or about 0.01% to or about 0.15%; retinol esters are most preferably used in an amount of from or about 0.02% to or about 2% (e.g., about 0.2%); retinoic acids are most preferably used in an amount of from or about 0.01% to or about 0.25%; tocopheryl-retinoate [tocopherol ester of retinoic acid (trans- or cis-)], other retinoic acid esters, adapalene {6-[3-(1-

adamantyl)-4-methoxyphenyl]-2-naphthoic acid}, and tazarotene are most preferably used in an amount of from about 0.01% to about 2%.

D. Sunscreens and Sunblocks

The compositions of the subject invention preferably contain a sunscreen or sunblock. These materials help shield the skin from the harmful effects of exposure to ultraviolet light, which can result in skin discoloration or pigmentation, excessive scaling and texture changes of the stratum corneum. Suitable sunscreens or sunblocks may be organic or inorganic.

A wide variety of conventional suncreening agents are suitable for use herein. Sagarin, et al., at Chapter VIII, pages 189 et seq., of Cosmetics Science and Technology (1972), discloses numerous suitable agents, and is incorporated herein by reference. Specific suitable suncreening agents include, for example: p-aminobenzoic acid, its salts and its derivatives (ethyl, isobutyl, glyceryl esters; p-dimethylaminobenzoic acid); anthranilates (i.e., o-amino-benzoates; methyl, menthyl, phenyl, benzyl, phenylethyl, linalyl, terpinyl, and cyclohexenyl esters); salicylates (amyl, phenyl, octyl, benzyl, menthyl, glyceryl, and di-pro-pyleneglycol esters); cinnamic acid derivatives (menthyl and benzyl esters, a-phenyl cinnamionitrile; butyl cinnamoyl pyruvate); dihydroxycinnamic acid derivatives (umbelliferone, methylumbelliferone, methylaceto-umbelliferone); trihydroxy-cinnamic acid derivatives (esculetin, methylesculetin, daphnetin, and the glucosides, esculin and daphnin); hydrocarbons (diphenylbutadiene, stilbene); dibenzalacetone and benzalacetophenone; naphtholsulfonates (sodium salts of 2-naphthol-3,6-disulfonic and of 2-naphthol-6,8-disulfonic acids); di-hydroxynaphthoic acid and its salts; o- and p-hydroxybiphenyldisulfonates; coumarin derivatives (7-hydroxy, 7-methyl, 3-phenyl); diazoles (2-acetyl-3-bromoindazole, phenyl benzoxazole, methyl naphthoxazole, various aryl benzothiazoles); quinine salts (bisulfate, sulfate, chloride, oleate, and tannate); quinoline derivatives (8-hydroxyquinoline salts, 2-phenylquinoline); hydroxy- or methoxy-substituted benzophenones; uric and violuric acids; tannic acid and its derivatives (e.g., hexaethylether); (butyl carbotol) (6-propyl piperonyl) ether; hydroquinone; benzophenones (oxybenzene, sulisobenzene, dioxybenzene, benzoescorcinol, 2,2',4,4'-tetrahydroxybenzophenone, 2,2'-dihydroxy-4,4'-dimethoxybenzophenone, octabenzene; 4-isopropylidibenzoylmethane; butylmethoxydibenzoylmethane; etocrylene; [3-(4'-methylbenzylidene bornan-2-one) and 4-isopropyl-di-benzoylmethane.

Of these, 2-ethylhexyl-p-methoxycinnamate, 4,4'-t-butyl methoxydibenzoyl-methane, 2-hydroxy-4-methoxybenzophenone, octyldimethyl-p-aminobenzoic acid, digalloyltriolate, 2,2-dihydroxy-4-methoxybenzophenone, ethyl-4-(bis(hydroxy-propyl))aminobenzoate, 2-ethylhexyl-2-cyano-3,3-diphenylacrylate, 2-ethylhexyl-salicylate, glyceryl-p-aminobenzoate, 3,3,5-tri-methylcyclohexylsalicylate, methylanthranilate, p-dimethyl-aminobenzoic acid or aminobenzoate, 2-ethylhexyl-p-dimethyl-amino-benzoate, 2-phenylbenzimidazole-5-sulfonic

acid, 2-(p-dimethylaminophenyl)-5-sulfonicbenzoxazoic acid and mixtures of these compounds, are preferred.

More preferred sunscreens useful in the compositions useful in the subject invention are 2-ethylhexyl-p-methoxycinnamate, butylmethoxydibenzoylmethane, 2-hydroxy-4-methoxybenzo-phenone, octyldimethyl-p-aminobenzoic acid and mixtures thereof.

Also particularly useful in the compositions are sunscreens such as those disclosed in U.S. Patent No. 4,937,370 issued to Sabatelli on June 26, 1990, and U.S. Patent No. 4,999,186 issued to Sabatelli & Spirmak on March 12, 1991, both of which are incorporated herein by reference. The suncreening agents disclosed therein have, in a single molecule, two distinct chromophore moieties which exhibit different ultra-violet radiation absorption spectra. One of the chromophore moieties absorbs predominantly in the UVB radiation range and the other absorbs strongly in the UVA radiation range.

Preferred members of this class of suncreening agents are 4-N,N-(2-ethylhexyl)methylaminobenzoic acid ester of 2,4-dihydroxybenzophenone; N,N-di-(2-ethylhexyl)-4-aminobenzoic acid ester with 4-hydroxydibenzoylmethane; 4-N,N-(2-ethylhexyl)methylaminobenzoic acid ester with 4-hydroxydibenzoylmethane; 4-N,N-(2-ethylhexyl)methylaminobenzoic acid ester of 2-hydroxy-4-(2-hydroxyethoxy)benzophenone; 4-N,N-(2-ethylhexyl)-methylaminobenzoic acid ester of 4-(2-hydroxyethoxy)dibenzoylmethane; N,N-di-(2-ethylhexyl)-4-aminobenzoic acid ester of 2-hydroxy-4-(2-hydroxyethoxy)benzophenone; and N,N-di-(2-ethylhexyl)-4-aminobenzoic acid ester of 4-(2-hydroxyethoxy)dibenzoylmethane and mixtures thereof.

Suitable inorganic sunscreens or sunblocks include metal oxides, e.g., zinc oxide and titanium dioxide. For example, the use of a titanium dioxide in topical sunscreen compositions that is applicable to the present invention is described in copending application Serial No. 08/448,942, filed on May 24, 1995, in the names of Jiang Yue, Lisa R. Dew and Donald L. Bissett, incorporated herein by reference.

A safe and effective amount of the sunscreen or sunblock is used, typically from or about 1% to or about 20%, more typically from or about 2% to or about 10%. Exact amounts will vary depending upon the sunscreen chosen and the desired Sun Protection Factor (SPF, a measure of erythema protection, primarily UVB protection) or UVA protection factor.

An agent may also be added to any of the compositions useful in the subject invention to improve the skin substantivity of those compositions, particularly to enhance their resistance to being washed off by water, or rubbed off. A preferred agent which will provide this benefit is a copolymer of ethylene and acrylic acid. Compositions comprising this copolymer are disclosed in U.S. Patent 4,663,157, Brock, issued May 5, 1987, which is incorporated herein by reference.

#### E. Chelators

As used herein, "chelating agent" means an active agent capable of removing a metal ion from a system by forming a complex so that the metal ion cannot readily participate in or catalyze chemical reactions. The inclusion of a chelating agent is especially useful for providing protection against UV radiation which can contribute to excessive scaling or skin texture changes and against other environmental agents which can cause skin damage.

A safe and effective amount of a chelating agent may be added to the compositions of the subject invention, preferably from or about 0.1% to or about 10%, also preferably from or about 1% to or about 5%, of the composition. Exemplary chelators that are useful herein are disclosed in U.S. Patent No. 5,487,884, issued 1/30/96 to Bissett et al.; International Publication No. 91/16035, Bush et al., published 10/31/95; and International Publication No. 91/16034, Bush et al., published 10/31/95; all incorporated herein by reference. Preferred chelators useful in compositions of the subject invention are furildioxime, furilmonoxime, and derivatives thereof.

F. Skin Lightening Agents

The compositions of the present invention may comprise a conventional skin lightening agent. When used, the compositions preferably comprise from or about 0.1% to or about 10%, more preferably from or about 0.2% to or about 5%, also preferably from or about 0.5% to or about 3%, of such agents. Suitable other skin lightening agents include those known in the art, including kojic acid, arbutin, niacinamide, ascorbic acid and derivatives thereof. Skin lightening agents suitable for use herein also include those described in copending patent application Serial No.08/390,152, filed on February 24, 1995 in the names of Kalla L. Kvalnes, Mitchell A. DeLong, Barton J. Bradbury, Curtis B. Motley, and John D. Carter, corresponding to PCT Application No. U.S. 95/02809, filed 3/1/95, published 9/8/95; incorporated herein by reference. Magnesium ascorbyl phosphate and niacinamide are preferred.

G. Humectants, Moisturizers, Occlusives, and Skin Conditioners

The compositions of the present invention may further comprise a humectant, moisturizing agent, occlusive or other skin conditioning agent. A variety of these materials can be employed and each can be present at a level of from or about 0.1% to or about 20%, more preferably from or about 1% to or about 10%, and most preferably from or about 2% to or about 5%. These materials include guanidine; glycolic acid and glycolate salts (e.g. ammonium and quaternary alkyl ammonium); lactic acid and lactate salts (e.g. ammonium and quaternary alkyl ammonium); aloe vera in any of its variety of forms (e.g., aloe vera gel); polyhydroxy alcohols such as sorbitol, glycerol, diglycerol, hexanetriol, butanetriol, propylene glycol, butylene glycol, hexylene glycol and the like; polyethylene glycols; sugars and starches; sugar and starch derivatives (e.g., alkoxylated glucose); hyaluronic acid; lactamide monoethanolamine;



acetamide monoethanolamine; betaine (trimethyl glycine); urea; tranexamic acid; and mixtures thereof.

Also useful herein are the propoxylated glycerols described in U.S. Patent No. 4,976,953, which description is incorporated herein by reference.

Also useful are various C<sub>1</sub>-C<sub>30</sub> monoesters and polyesters of sugars and related materials. These esters are derived from a sugar or polyol moiety and one or more carboxylic acid moieties. Depending on the constituent acid and sugar, these esters can be in either liquid or solid form at room temperature. Examples of liquid esters include: glucose tetraoleate, the glucose tetraesters of soybean oil fatty acids (unsaturated), the mannose tetraesters of mixed soybean oil fatty acids, the galactose tetraesters of oleic acid, the arabinose tetraesters of linoleic acid, xylose tetralinoleate, galactose pentaoleate, sorbitol tetraoleate, the sorbitol hexaesters of unsaturated soybean oil fatty acids, xylitol pentaoleate, sucrose tetraoleate, sucrose pentaoleate, sucrose hexaoleate, sucrose hepatoleate, sucrose octaoleate, and mixtures thereof. Examples of solid esters include: sorbitol hexaester in which the carboxylic acid ester moieties are palmitoleate and arachidate in a 1:2 molar ratio; the octaester of raffinose in which the carboxylic acid ester moieties are linoleate and behenate in a 1:3 molar ratio; the heptaester of maltose wherein the esterifying carboxylic acid moieties are sunflower seed oil fatty acids and lignocerate in a 3:4 molar ratio; the octaester of sucrose wherein the esterifying carboxylic acid moieties are oleate and behenate in a 2:6 molar ratio; and the octaester of sucrose wherein the esterifying carboxylic acid moieties are laurate, linoleate and behenate in a 1:3:4 molar ratio. A preferred solid material is sucrose polyester in which the degree of esterification is 7-8, and in which the fatty acid moieties are C<sub>18</sub> mono- and/or di-unsaturated and behenic, in a molar ratio of unsaturates:behenic of 1:7 to 3:5. A particularly preferred solid sugar polyester is the octaester of sucrose in which there are about 7 behenic fatty acid moieties and about 1 oleic acid moiety in the molecule. The ester materials are further described in, U.S. Patent No. 2,831,854, U.S. Patent No. 4,005,196, to Jandacek, issued January 25, 1977; U.S. Patent No. 4,005,195, to Jandacek, issued January 25, 1977, U.S. Patent No. 5,306,516, to Letton et al., issued April 26, 1994; U.S. Patent No. 5,306,515, to Letton et al., issued April 26, 1994; U.S. Patent No. 5,305,514, to Letton et al., issued April 26, 1994; U.S. Patent No. 4,797,300, to Jandacek et al., issued January 10, 1989; U.S. Patent No. 3,963,699, to Rizzi et al, issued June 15, 1976; U.S. Patent No. 4,518,772, to Volpenhein, issued May 21, 1985; and U.S. Patent No. 4,517,360, to Volpenhein, issued May 21, 1985; all of which are incorporated by reference herein in their entirety. Other skin conditioning agents and/or occlusives useful in the compositions of the present invention include petrolatum, lanolin, cocoa butter, mineral oil, and silicones.

#### H. Organic Hydroxy Acids

The compositions of the present invention may comprise an organic hydroxy acid such as salicylic acid, glycolic acid, lactic acid, 5-octanoylsalicylic acid, hydroxyoctanoic acid, hydroxycaprylic acid, and lanolin fatty acids. Preferred concentrations of the organic hydroxy acid range from or about 0.1% to or about 10%, more preferably from or about 0.2% to or about 5%, also preferably from or about 0.5% to or about 2%. Salicylic acid is preferred. The organic hydroxy acids enhance the skin appearance benefits of the present invention. For example, the organic hydroxy acids tend to improve the texture of the skin.

I. Desquamation Agents/Exfoliants

A safe and effective amount of a desquamation agent may be added to the compositions of the subject invention, preferably from or about 0.1% to or about 10%, more preferably from or about 0.2% to or about 5%, also preferably from or about 0.5% to or about 4% of the composition. Desquamation agents enhance the skin appearance benefits of the present invention. For example, the desquamation agents tend to improve the texture of the skin (e.g., smoothness). A variety of desquamation agents are known in the art and are suitable for use herein, including but not limited to the organic hydroxy agents described above, amino acids (e.g., alanine and serine), and zwitterionic surfactants (e.g., the betaines). One desquamation system that is suitable for use herein comprises salicylic acid and certain zwitterionic surfactants and is described in copending patent application Serial No. 08/209,401, filed on March 9, 1994 in the name of Bissett, corresponding to PCT Application No. 94/12745, filed 11/4/94, published 5/18/95, each incorporated herein by reference.

J. Antimicrobial Agents

As used herein, "antimicrobial agent" means a compound capable of destroying microbes, preventing the development of microbes or preventing the pathogenic action of microbes. Antimicrobial agents are useful, for example, in controlling acne and are therefore preferred for use in compositions intended for treating acne. A safe and effective amount of an antimicrobial agent may be added to compositions of the subject invention, preferably from or about 0.001% to or about 10%, more preferably from or about 0.01% to or about 5%, also from or about 0.05% to or about 2% or from or about 0.05% to or about 1% of the compositions. Preferred antimicrobial agents useful in the subject invention are benzoyl peroxide, erythromycin, tetracycline, clindamycin, azelaic acid, and sulfur resorcinol.

K. Other Optional Components

The compositions of the present invention may also include natural extracts, including those known in the topical personal care art. Such extracts enhance the skin appearance benefits of the present invention, and are preferably used in a safe and effective amount, more preferably an amount of from or about 0.1% to or about 20%, even more preferably from or about 0.5% to or about 10%, also from or about 1% to or about 5%. Such extracts include plant and fungal

extracts such as extracts of the plant *Centella asiatica*, yeast and rice bran. Suitable extracts of these types are commercially available, e.g., from Maruzen Pharmaceuticals Co. LTD. of Hiroshima, Japan.

Compounds which are known to stimulate the production of collagen can also be used in the present invention. Such compounds include Factor X (kinetin), Factor Z (zeatin), n-methyl taurine, dipalmitoyl hydroxyproline, palmitoyl hydroxy wheat protein, biopeptide CL (palmitoyl glycyl-histidyl-lysine), ASC III (Amplifier of Synthesis of Collagen III, E. Merck, Germany), beta glucan, and vitamin B<sub>3</sub> compounds (e.g., niacinamide, tocopherol nicotinate, inositol hexanicotinate). Such compounds tend to improve the regulation of skin texture discontinuities associated with skin aging.

The compositions hereof can also include natural ceramides or the like, for example, ceramide 1 - 6, ceramide analogs or precursors (e.g., L-serine, 3-dehydrosphinganine, sphinganine, sphingosine, fatty acid amides, palmitoyl co-enzyme A), and/or co-factors involved in ceramide synthesis (e.g., pyridoxine, pyridoxal, pyridoxamine, riboflavin, pantothenic acid, co-enzyme A, acetyl co-enzyme A, flavin adenine dinucleotide (FAD), reduced FAD (FADH<sub>2</sub>), nicotinamide adenine dinucleotide (NAD), reduced NAD (NADH), nicotinamide adenine dinucleotide phosphate (NADP), and reduced NADP (NADPH)).

The compositions can also contain an oil absorbent such as are known in the art, e.g. clays (e.g. bentonite) and polymeric absorbents (e.g., MICROSPONGES 5647 and POLYTRAP, both commercially available from Advanced Polymer Systems, Inc. of Redwood City, California, USA. MICROSPONGES 5647 is a polymer mixture derived from styrene, methyl methacrylate, and hydrogel acrylate/methacrylate.

Compositions hereof can also contain a thickener. The thickener tends to enhance the physical stability of the composition. A variety of thickeners are known in the art and are useful herein. The concentration of thickener is generally from or about 0.05% to or about 5%, preferably 0.1% to or about 4%, more preferably 0.5% to or about 3%. Where the composition contains an electrolyte, preferred thickeners are those which are substantially insensitive to electrolytes. Preferred thickeners of this type are selected from polyalkylene glycol-based polyurethane polymers such as Polyolprepolymer-2, 14, and 15 from Penederm (Foster City, California), each having the CAS name poly[oxy(methyl-1,2-ethanediyl)], alpha-hydro-omega-hydroxypolymer. In addition to thickening, these polymers aid in film-forming and substantivity of the composition, deposition of actives, provide emolliency, and enhance spreadability and tactile skin smoothness. Other thickeners compatible with electrolytes include silicone polymers (polydimethylsiloxanes); for example, dimethicone, dimethiconol, from Dow Corning, Midland, Michigan. Synthetic waxes (mixtures of long carbon chain wax esters, glycerides, and fatty acids; for example, the SYNCROWAX family, from Croda (Parsippany,

New Jersey)) can also be used. Organoclays can also be used as thickeners. Suitable organoclays include reaction products of an organic quaternary amine with hectorite clay, e.g., organoclays commercially available under the tradename "Bentones" from Rheox (Hightstown, New Jersey). Derivatives of castor oil are also useful as thickeners; for example, Thixcin R, a powdered, organic derivative of castor oil, also from Rheox.

Other examples of additional components useful herein include the following: water-soluble vitamins and derivatives thereof; polyethyleneglycols and polypropyleneglycols; polymers for aiding the film-forming properties and substantivity of the composition (such as a copolymer of eicosene and vinyl pyrrolidone, an example of which is available from GAF Chemical Corporation as Ganex<sup>®</sup> V-220; also polyalkylene glycol-based polyurethane polymers such as Polyolprepolymer-2, 14, and 15 from Penederm). Also useful are crosslinked and noncrosslinked nonionic and cationic polyacrylamides [e.g., Salcare SC92 which has the CTFA designation polyquaternium 32 (and) mineral oil, and Salcare SC 95 which has the CTFA designation polyquaternium 37 (and) mineral oil (and) PPG-1 trideceth-6, and the nonionic Seppi-Gel polyacrylamides available from Seppic Corp. of Fairfield, NJ. Also useful are crosslinked and uncrosslinked carboxylic acid polymers and copolymers such as those containing one or more monomers derived from acrylic acid, substituted acrylic acids, and salts and esters of these acrylic acids and the substituted acrylic acids, wherein the crosslinking agent contains two or more carbon-carbon double bonds and is derived from a polyhydric alcohol (examples useful herein include the carbomers, which are homopolymers of acrylic acid crosslinked with allyl ethers of sucrose or pentaerytritol and which are available as the Carbopol<sup>®</sup> 900 series from B.F. Goodrich, and copolymers of C<sub>10-30</sub> alkyl acrylates with one or more monomers of acrylic acid, methacrylic acid, or one of their short chain (i.e., C<sub>1-4</sub> alcohol) esters, wherein the crosslinking agent is an allyl ether of sucrose or pentaerytritol, these copolymers being known as acrylates/C<sub>10-30</sub> alkyl acrylate crosspolymers and are commercially available as Carbopol<sup>®</sup> 1342, Pemulen TR-1, and Pemulen TR-2, from B.F. Goodrich). These carboxylic acid polymers and copolymers are more fully described in U.S. Patent No. 5,087,445, to Haffey et al., issued February 11, 1992; U.S. Patent No. 4,509,949, to Huang et al., issued April 5, 1985; U.S. Patent No. 2,798,053, to Brown, issued July 2, 1957; which are incorporated by reference herein. See also, CTFA International Cosmetic Ingredient Dictionary, fourth edition, 1991, pp. 12 and 80; which is also incorporated herein by reference.

Also useful herein are aesthetic components such as fragrances, pigments, colorings, essential oils, skin sensates, astringents, skin soothing agents, skin healing agents and the like, nonlimiting examples of these aesthetic components include clove oil, menthol, camphor, eucalyptus oil, eugenol, menthyl lactate, witch hazel distillate, bisabolol, dipotassium glycyrrhizinate and the like.

In a particularly preferred embodiment, the compositions of the present invention contain, in addition to tocopherol sorbate, one or more of an anti-inflammatory agent, an anti-oxidant/radical scavenger, and a retinoid, more preferably at least one of each of these ingredients.

#### Preparation of Compositions

The compositions of the present invention are generally prepared by conventional methods such as are known in the art of making topical compositions. Such methods typically involve mixing of the ingredients in one or more steps to a relatively uniform state, with or without heating, cooling, application of vacuum, and the like.

#### Methods for Lightening Skin

The compositions of the present invention are useful for lightening mammalian skin (especially human skin, more especially facial and hand skin). The compositions are especially useful for lightening hyperpigmented regions of skin.

The method of lightening skin (including hyperpigmented regions) involves topically applying to the skin a safe and effective amount of a composition of the present invention. The amount of the composition which is applied, the frequency of application and the period of use will vary widely depending upon the level of tocopherol sorbate and/or other components of a given composition and the level of lightening desired, e.g., in light of the level of skin pigmentation present in the subject and the rate of further skin pigmentation.

In a preferred embodiment, the composition is chronically applied to the skin. By "chronic topical application" is meant substantially continuous topical application of the composition over an extended period during the subject's lifetime, preferably for a period of at least about one week, more preferably for a period of at least about one month, even more preferably for at least about three months, even more preferably for at least about six months, and still more preferably for at least about one year. While benefits are obtainable after various maximum periods of use (e.g., two, five, ten or twenty years), it is preferred that chronic application continue throughout the subject's lifetime. Typically applications would be on the order of about once or twice per day over such extended periods, however application rates can vary, e.g., from about once per week up to about three times per day or more.

A wide range of quantities of the compositions of the present invention can be employed to provide a skin lightening benefit. Quantities of the present compositions which are typically applied per application are from about 0.1 mg/cm<sup>2</sup> skin to about 10 mg/cm<sup>2</sup> skin. A particularly useful application amount is about 2 mg/cm<sup>2</sup> skin.

The method of lightening skin is preferably practiced by applying a composition in the form of a skin lotion, cream, cosmetic, or the like which is intended to be left on the skin for some esthetic, prophylactic, therapeutic or other benefit. After applying the composition to the

skin, it is preferably left on the skin for a period of at least about 15 minutes, more preferably at least about 30 minutes, even more preferably at least about 1 hour, most preferably for at least several hours, e.g., up to about 12 hours.

The compositions of the present invention are also useful for regulating mammalian skin condition more generally (especially human skin, more especially facial and/or hand skin), including signs of skin aging, and visible and/or tactile discontinuities in skin associated with skin aging. Such regulation includes prophylactic and/or therapeutic regulation. Regulating skin condition involves topically applying to the skin a safe and effective amount of a composition of the present invention. The amount of the composition which is applied, the frequency of application and the period of use will vary widely depending upon the level of tocopherol sorbate and/or other components of a given composition and the level of regulation desired, e.g., in light of the level of skin aging present in the subject and the rate of further skin aging. Regulating skin condition involves steps in accordance with those described for skin lightening.

#### Examples

The composition embodiments of the present invention are illustrated in the following non-limiting examples. All parts, percentages, and ratios used herein are by weight unless otherwise specified.

#### Example 1

An oil-in-water emulsion containing the following ingredients is prepared.

component	weight %
Glycerine	4
EDTA disodium	0.12
Water	40.98
Cetearyl alcohol	10
Ceteareth-20	2
Mineral oil, light white	3
Propyl p-hydroxybenzoate	0.15
Polyolprepolymer-2	3
Bisabolol	0.25
Stearyl glycyrrhetinate	0.2
Tocopherol, ascorbyl palmitate, citric acid, lecithin, mono & diglycerides (OXYNEX LM from Rona EM Industries, Hawthorne, New York)	0.01
Methyl p-hydroxybenzoate	0.25

Water	30
Mg Ascorbyl Phosphate	3
Retinyl palmitate w/ tocopherol available as Vitamin A palmitate Type P 1.7/E from Hoffmann LaRoche, Belvidere, New Jersey	0.44
Tocopherol sorbate	2
Benzyl alcohol	0.5
Fragrance	0.1

Combine the glycerine, EDTA and water, heat to about 70 °C and mix until uniform with propeller at about 400 rpm. Combine the Cetearyl alcohol, Ceteareth-20, Mineral oil, Propyl p-hydroxybenzoate, Polyolprepolymer-2, Bisabolol, Stearyl glycyrrhetinate, Oxydex, heat until all solids melt and mix until uniform with propeller at about 400 rpm (oil phase). Add the methyl p-hydroxybenzoate to the aqueous mixture while mixing at about 1200 rpm, 70 °C. Slowly add the oil phase at about 70° C to the aqueous mixture, and mix until uniform with propeller at about 400 rpm. Cool the resulting emulsion to about 40 °C while mixing at reduced speed. Separately premix the magnesium ascorbyl phosphate and water in a 1:10 mixture by mixing above 1000 rpm and at less than 45 °C. Add this premix to the emulsion while stirring at reduced speed. Cool to about 30-35 °C. Add the remaining ingredients one at a time while mixing at reduced speed and low shear. Adjust pH as required (preferably 6 to 8).

Apply the composition to a subject's facial skin at the rate of 2 mg composition/cm<sup>2</sup> skin once or twice daily for a period of at least 3-6 months to lighten hyperpigmented spots and produce a less blotchy, more even skin color and skin clarity.

#### Example 2

A topical composition is prepared from the following ingredients using conventional methods.

component	weight %
Water	69.2
Disodium EDTA	0.1
Methyl Paraben	0.2
Glycerin	3.0
Benzyl alcohol	0.3
Ethanol	3.0
Hexylene glycol	2.0
Cyclomethicone-Dow Corning 345 fluid	15.0

Polyglyceryl-4 Isostearate, cetyl Dimethicone Copolyol, Hexyl Laurate (Abil WE09)	2.5
cyclomethicone and dimethicone copolyol - Dow Corning 3225C	2.5
Tocopherol sorbate	2.0
Fragrance	0.2

Mix the water, disodium EDTA, glycerin, ethanol, and hexylene glycol at about 400 rpm. Dissolve the methylparaben in the benzyl alcohol and add to the aqueous phase, mixing above 1000 rpm. Separately mix the cyclomethicone, Abil WE09, Dow Corning 3225C and tocopherol sorbate. Add the aqueous mixture to the silicone mixture very slowly while mixing with minimum shear. Add fragrance while mixing with minimum shear.

Apply the composition to a subject's facial skin at the rate of 2 mg composition/cm<sup>2</sup> skin once or twice daily for a period of at least 3-6 months to lighten hyperpigmented spots and produce a less blotchy, more even skin color and skin clarity.

### Example 3

A topical composition is prepared from the following ingredients using conventional methods.

component	weight %
Water	76.65
Cetyl Hydroxyethyl cellulose-(Polysurf 67)	0.15
Disodium EDTA	0.15
Glycerin	5.0
Methyl paraben	0.25
Panthenol DL	0.5
Cetyl Ricinoleate (Naturechem CR)	3.0
Caprylic/capric triglyceride (Myritrol 318)	1.5
Myristyl Myristate (Schercomol MM)	1.5
Mineral Oil	2.0
Titanium Dioxide	0.75
Propyl paraben	0.1
Stearyl alcohol	0.5
Cetyl alcohol	0.5
Behenyl alcohol	0.5
Steareth-2 (Brij 72)	1.05
Glyceryl monostearate-PEG 30 stearate (Arlatone 983)	1.05



Distearyldimonium Chloride (Varisoft TA-100)	0.25
Tocopherol sorbate	2.0
Dow 2-1068	2.0
Benzyl Alcohol	0.5
Fragrance	0.1

Mix the water, cetyl hydroxyethyl cellulose, disodium EDTA, glycerin, and panthenol DL at about 400 rpm. Heat this mixture to about 70 °C while mixing at about 400 rpm. Add the methylparaben while mixing above 1000 rpm. Separately mix the cetyl ricinoleate, caprylic/capric triglycerides, amyristyl myristate, mineral oil, titanium dioxide, propylparaben, stearyl alcohol, cetyl alcohol, behenyl alcohol, steareth-2, glyceryl monostearate-PEG 30 stearate, distearyldimonium chloride and tocopherol sorbate (oil phase). Heat this mixture to about 70 °C while mixing below about 200 rpm. Slowly add the oil phase at about 70 °C to the aqueous mixture, and mix until uniform with propeller at about 400 rpm. Cool the resulting emulsion below about 40 °C while mixing at reduced speed. Add the Dow 2-1068, benzyl alcohol, and fragrance to the emulsion. Cool the mixture to room temperature while mixing at low speed and low shear. Adjust the final pH if necessary with sodium hydroxide.

Apply the composition to a subject's facial skin at the rate of 2 mg composition/cm<sup>2</sup> skin once or twice daily for a period of at least 3-6 months to lighten hyperpigmented spots and produce a less blotchy, more even skin color and skin clarity.

While particular embodiments of the subject invention have been described, it will be obvious to those skilled in the art that various changes and modifications of the subject invention can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of the invention.

**What is claimed is:**

1. A method of lightening hyperpigmented regions of skin, comprising topically applying to the skin a safe and effective amount of a composition comprising (a) an active effective for lightening hyperpigmented regions of skin and (b) a topical carrier, the active consisting essentially of tocopherol sorbate.
2. The method of Claim 1 wherein the composition comprises from 0.01% to 10%, preferably 0.1% to 5% of tocopherol sorbate.
3. The method of Claim 1 or Claim 2 wherein the composition further comprises a compound selected from the group consisting of anti-inflammatory agents, anti-oxidants/radical scavengers, retinoids, niacinamide and combinations thereof.
4. The method according to any of Claims 1 to 3 wherein the antiinflammatory agent is selected from the group consisting of bisabolol, chamomile extract, compounds of the Licorice (*Glycyrrhiza glabra*) family and derivatives thereof, panthenol, methyl salicylate, aloe, allantoin and mixtures thereof; wherein the anti-oxidant/radical scavenger is an ascorbic acid derivative, preferably magnesium ascorbyl phosphate, and mixtures thereof; and wherein the retinoid is selected from the group consisting of retinol palmitate, retinol acetate, retinol propionate, retinol, and mixtures thereof.
5. The method according to any of Claims 1 to 4 wherein the topical carrier comprises an oil-in-water emulsion.
6. The method according to any of Claims 1 to 5 wherein the emulsion comprises
  - (a) a saturated fatty alcohol of the formula  $\text{CH}_3(\text{CH}_2)_p\text{CH}_2\text{OH}$ , wherein  $p$  is an integer greater than about 10, preferably the fatty alcohol is selected from stearyl alcohol, cetyl alcohol and cetearyl alcohol; and
  - (b) an ethoxylated ether of a saturated fatty alcohol having the formula  $\text{CH}_3(\text{CH}_2)_m\text{CH}_2(\text{OCH}_2\text{CH}_2)_n(\text{OH})$ , wherein " $m$ " is an integer greater than about 10 and " $n$ " is on average an integer of greater than about 10, preferably the ether is selected

from Ceteareth-n, Steareth-n, and Ceteth-n, wherein n is the average number of moles of ethylene oxide in the ether.

7. A composition suitable for lightening mammalian skin, comprising:
  - (a) tocopherol sorbate;
  - (b) an anti-inflammatory agent, preferably the anti-inflammatory agent is selected from bisabolol, chamomile extract, compounds of the Licorice (*Glycyrrhiza glabra*) family and derivatives thereof, panthenol, methyl salicylate, aloe, allantoin and mixtures thereof;
  - (c) an anti-oxidant/radical scavenger, preferably the anti-oxidant/radical scavenger is selected from ascorbic acid derivatives, more preferably wherein the anti-oxidant/radical scavenger is magnesium ascorbyl phosphate;
  - (d) a retinoid, preferably the retinoid is selected from retinol palmitate, retinol acetate, retinol propionate, retinol and mixtures thereof; and
  - (e) a topical carrier.
8. The composition of Claim 7 wherein the topical carrier comprises an oil-in-water emulsion.
9. The composition of Claim 7 or Claim 8 wherein the emulsion comprises
  - (a) a saturated fatty alcohol of the formula  $\text{CH}_3(\text{CH}_2)_p\text{CH}_2\text{OH}$ , wherein p is an integer greater than about 10, preferably the fatty alcohol is selected from stearyl alcohol, cetyl alcohol and cetearyl alcohol; and
  - (b) an ethoxylated ether of a saturated fatty alcohol having the formula  $\text{CH}_3(\text{CH}_2)_m\text{CH}_2(\text{OCH}_2\text{CH}_2)_n(\text{OH})$ , wherein "m" is an integer greater than about 10 and "n" is on average an integer of greater than about 10, preferably the ether is selected from Ceteareth-n, Steareth-n, and Ceteth-n, wherein n is the average number of moles of ethylene oxide in the ether.
10. A method of lightening skin by regulating melanin in skin, comprising topically applying to the skin a safe and effective amount of a composition comprising (a) an

active effective for lightening hyperpigmented regions of skin and (b) a topical carrier, the active consisting essentially of tocopherol sorbate.

# INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/US 98/02380

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 313 304 A (PROCTER & GAMBLE) 26 April 1989	1-6, 10
Y	see page 1-5, line 15 see page 8, line 11-12 see page 8, line 29-30 see page 17, line 9-33 ---	7-9
X	EP 0 313 303 A (PROCTER & GAMBLE) 26 April 1989 see page 1-5, line 50 see page 6, line 47-50 see page 7, line 15-20 see page 9, line 53-54 --- -/--	1-6, 10



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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# INTERNATIONAL SEARCH REPORT

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>WO 95 34280 A (PROCTER &amp; GAMBLE) 21  December 1995  cited in the application  see page 10, line 1-6  see page 14, line 21-37  see page 15, line 1-3  see page 16, line 1-16  -----</p>	7-9

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/02380

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